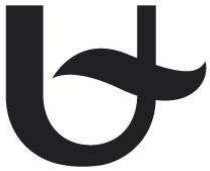

Universiteit Antwerpen

Faculteit Geneeskunde

A DIAGNOSTIC AND SURGICAL APPROACH TO THE TONGUEBASE AND HYPOPHARYNX IN OBSTRUCTIVE SLEEP APNEA SYNDROME

EEN DIAGNOSTISCHE EN HEELKUNDIGE BENADERING VAN DE TONGBASIS EN HYPOFARYNX BIJ OBSTRUCTIEF SLAAP APNEU SYNDROOM

Proefschrift voorgelegd tot het behalen van de graad van Doctor in de Medische Wetenschappen aan de Universiteit Antwerpen te verdedigen door

Evert HAMANS

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Promotoren: Prof. Dr. P. Van de Heyning
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A diagnostic and surgical approach to the tonguebase and hypopharynx in obstructive sleep apnea syndrome

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Aan mijn vader…

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Chapter 1

Introduction and aims of this thesis

Introduction and aims of this thesis

Obstructive sleep apnea syndrome (OSAS) is a sleep-related breathing disorder characterized by repetitive obstruction of the upper airway (UA) during sleep resulting in a decrease or a complete cessation of oronasal airflow that are called respiratory events. Collapse can occur at different levels in the UA: from nasopharynx to epiglottis. It affects 4% of men and 2% of women in the middle aged population (1). OSAS is caused by unstable breathing during sleep which causes an increase in UA resistance and collapsibility, discoordination of local reflex mechanisms and a compromised UA anatomy (2).
Untreated OSAS causes decreased neurocognitive functioning and increased cardiovascular and cerebrovascular risks (3).

The principle nighttime complaint of OSAS is loud snoring and the main daytime complaint is excessive daytime sleepiness. Patients who present these complaints need a diagnostic work-up including complete history taking, clinical examination and sleep registration (4).

A variety of options are available for the treatment of OSAS, depending on severity of the disease, upper airway anatomy and the patients preference. General measures like weight loss, prevention of alcohol and sedative medication in the evening, smoking habits and sleep positioning therapy should be applied first. The gold standard treatment for OSAS is continuous positive airway pressure (CPAP)(5), which prevents ventilatory events by pneumatically splinting the upper airway. Although the efficacy of CPAP in improving nighttime and daytime complaints and cardiovascular disease has been demonstrated in randomised controlled trials (6), an important group of patients do not tolerate or show poor adherence to this treatement because of side effects or lack of substantial benefit (7). In these patients, treatment with a mandibular advancement device or surgical treatment can be considered (8).

Upper airway surgery for OSAS is frequently performed since the introduction of uvulopalatopharyngoplasty (UPPP)(9). The overall success rate was 40.7%, although among patients with clinical signs of tonguebase collapse the success rate was only 5.3% (10). These data support the hypothesis that UPPP might be a suitable treatment in patients with a clear palatal collapse of the upper airway, but not suitable for patients with multilevel (palatal and tonguebase) or isolated tonguebase collapse. Upper airway evaluation for the detection and selection of patients with tonguebase collapse is therefore important.

Various methods are available to determine the site of upper airway obstruction during sleep in OSAS patients. These methods include both static and dynamic methods, performed during wakefulness or sleep. All of them have their specific limitations and advantages (11).

A routine ENT examination of the awake patient in a sitting position, including the Müller manoeuver gives limited information on the upper airway behaviour during sleep. Dimensions of the upper airway change during sleep because of muscle relaxation.

Therefore the examination of the upper airway can be complemented with a dynamic evaluation to determine the site and pattern of upper airway collapse during sleep.

Cephalometry and computed tomography can be performed during sleep (12) but they are static and unphysiological methods which are further limited by their side effects of irradiation. Magnetic resonance imaging may bypass the problem of irradiation, and ultra-fast sequencing may even provide dynamic study (13), but this method is entirely limited by costs and availability.

Several authors have used multi-sensor pressure catheters positioned in the UA to determine the site of collapse (14). One of the main advantages of this technique is that it can be applied simultaneously during a full overnight PSG. Using this technique, only the most distal site of obstruction is defined and no information about the lateral hypopharyngeal wall is obtained. Moreover, this technique needs qualified personel and is time consuming.

The ideal method would involve direct visualisation of the upper airway during natural sleep. Fiberoptic evaluation of the upper airway during natural sleep was described in the late seventies (15), but this is clearly limited by its requirement for an unnatural sleep laboratory environment, not to mention an unusually compliant sleeping patient.
So, the next best option would appear to be drug-induced sleep endoscopy. The feasibility, safety and outcome of drug-induced sleep endoscopy is studied in this thesis.

Since the introduction of UPPP, a variety of surgical procedures that address the tonguebase and hypopharynx are described in order to improve success rates of surgery for OSAS. The majority of these procedures are invasive, have substantial side effects and lack evidence based efficacy (16).
Expansion sphincter pharyngoplasty was described as a technique to stabilize the oropharyngeal lateral walls in patients with OSAS (17). Procedures addressing the hypopharyngeal lateral walls are inexistent.
Tonguebase procedures with substantial morbidity which are generally more invasive, like genioglossus advancement, partial tonguebase resection and maxillary advancement, are not discussed in this thesis since they do not compare with the new techniques studied in this thesis. These techniques are discussed in a recent review (16).
The following, less invasive procedures are routinely performed for the treatment of tonguebase obstruction in OSAS patients:

1. Tongue suspension with a suture through the tonguebase is not titratable, has substantial side effects (dysphagia, pain) and limited efficacy (18).
2. Hyoid suspension is invasive, has side effects (dysphagia) and limited efficacy (19).
3. Radiofrequency ablation of the tonguebase is not invasive, has limited side effects but limited efficacy was reported in the treatment of patients with moderate to severe OSAS (20).

Because of the limitations of the present procedures addressing the tonguebase and hypopharynx, new techniques for stabilisation of the tonguebase and hypopharyngeal lateral walls are evaluated in this thesis.

In order to evaluate new methods for detection and treatment of tonguebase- and hypopharyngeal collapse, the aims of this thesis are:

1. To provide a general overview of present procedures for diagnosis and treatment of obstructive sleep apnea with a focus on tonguebase- and hypopharyngeal collapse (chapter 2).
2. To evaluate the role of sleep endoscopy as a diagnostic tool for tonguebase- and hypopharyngeal collapse of the upper airway (chapter 3).
3. To evaluate feasibility, safety and efficacy of hyoid expansion as a new procedure for obstructive sleep apnea in patients with hypopharyngeal lateral wall collapse (chapter 4).
4. To evaluate feasibility, safety and histology of an adjustable tongue anchor for the treatment of obstructive sleep apnea in an animal model (chapter 5).
5. To evaluate feasibility, safety and efficacy of adjustable tongue advancement as an innovative procedure for obstructive sleep apnea in patients with tonguebase collapse (chapter 6).
6. To evaluate the effect of the position of the tongue anchor on the objective outcome measures in patients treated with adjustable tongue advancement (chapter 7).

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Chapter 2

Obstructive sleep apnea syndrome:

definition, pathophysiology, diagnosis and treatment

This chapter is based on the following publications:

Hamans E, Boudewyns A, De Backer W, Coen E, Verbraecken J, Van de Heyning P. Sleep related breathing disorders: the respiratory control system and its instability during sleep. Acta Otorhinolaryngologica Belg 1995;49:45-51

Hamans E, Van Cauwenberge P. De rol van uvulopalatofaryngoplastie bij slaap-gerelateerde ademhalingsstoornissen. Tijdschr voor Geneeskunde 1999;55:1510-1516.

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Pervernagie D, **Hamans E**, Van Cauwenberge P, Pauwels R. External nasal dilation reduces snoring in chronic rhinitis patients: a randomized controlled trial. Eur Respir J 2000;15:996-1000.

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Hamans E. Radiofrequentie volumereductie van de tongbasis voor obstructief slaapanpeusyndroom. Ned Tijdschr KNO Heelk 2004;10:19-23

Boudewyns A, Vanderveken O, **Hamans E**, Van de Heyning P. Surgery for obstructive sleep apnea: an otorhinolaryngologist's perspective. Int Journal Respir Care 2005;4:123-129.

1.Definition and epidemiology.

Sleep related breathing disorders are probably first described by Bickelmann and Burwell in 1956 (1). It was called Pickwickian Syndrome, after a description of a patient with obstructive sleep apnea syndrome (OSAS) by Charles Dickens in his novel The Pickwick Papers in 1837. OSAS itself was first described in the seventies by Christian Guilleminault (2).

According to the American Academy of Sleep Medicine, obstructive sleep apnea syndrome (OSAS) is defined by a combination of symptoms (e.g. excessive daytime sleepiness) and polysomnographic findings (3). Polysomnography should demonstrate a respiratory disturbance index (RDI) of five or more obstructed breathing events per hour of sleep. These events include any combination of apneas, hypopneas and respiratory effort related arousals (RERA's). Since the detection of RERA's requires more sensitive diagnostic monitoring techniques, the number of obstructed breathing events is usually quantified by the number of apneas and hypopneas per hour of sleep (apnea-hypopnea-index, AHI). Based on the AHI, OSAS may be classified as mild (AHI 5-15), moderate (AHI 15-30) or severe (AHI>30) (4). When the above stated recommendations are adopted, OSAS can be diagnosed in 2% of women and 4% of men in the middle-aged North-American population (5).

2. Clinical presentation

Obstructive sleep apnea is mainly characterized by loud snoring. A detailed description of the subject's snoring can usually raise the suspicion of the clinical diagnosis. Prevalence of snoring is high: 44% of men and 28% of women suffer from habitual snoring (5). Occasionally, however, snoring may not be so prominent even in the presence of severe sleep apnea. Excessive daytime sleepiness (EDS) is the principal daytime manifestation of OSAS. The suspicion of OSAS may also arise in the presence of witnessed apneas, chocking or gasping during sleep. This witnessed

abnormal respiration during sleep warrants referral to a sleep clinic. Although patients may present with snoring, EDS or witnessed apneas, or a combination of other symptoms suggestive for OSAS, none of these symptoms alone allow for an accurate diagnosis. Other symptoms are sometimes present in patients with OSAS: morning headache, nocturnal enuresis, cognitive disturbances, decrease of libido, dry mouth in the morning and restless sleep.

3. Consequences

Neurocognitive consequences

In OSAS, apneas and hypopneas are terminated by an arousal, to stop the respiratory event. Although the activity of the dilator muscle activity increases as apnea progresses, the increase is generally insufficient to re-establish pharyngeal patency. Thus, the patient repeatedly arouses from sleep throughout the night. The precise stimulus to arousal is debated. A combination of increasing respiratory effort, hypoxia or hypercapnia, and upper airway mechanoreceptor stimulation are involved (6).

The neurocognitive consequences of recurrent arousal include sleepiness, reduced performance in neuropsychological tests, lengthened reaction times, reduced creativity, decreased quality of life and increased traffic accidents (7).

Cardiovascular and cerebrovascular consequences

There is increasing evidence to support an independent association between OSAS and cardiovascular disease (8). Patients with drug-resistant hypertension may benefit from a referral to a sleep specialist, even if they do not show the classical symptoms of OSAS. The association is particularly strong for systemic arterial hypertension. The evidence for the association with ischaemic heart disease, heart failure, atrial fibrillation and cardiac sudden death is growing (9).

OSAS is also an important risk factor for stroke and transient ischaemic attacks (10). However, there is no evidence of a beneficial effect of CPAP treatment in the prevention of stroke.

4. Pathophysiology

The pathophysiology of OSAS is incompletely understood. However, it appears to involve aspects of both upper airway collapsibility and respiratory control stability.

Upper airway (UA) collapsibility is influenced by anatomical factors and UA dilator muscle activity.

The cross sectional area of patients with OSAS, even during wakefulness, is anatomically smaller than controls. This has been shown by computed tomography (11) and acoustic reflection techniques (12). Edema of the palatal mucosa and hyperplasia of the palatal epithelium contribute to upper airway narrowing (13). A narrowed pharyngeal airway will predispose to the generation of marked negative intraluminal pressures during inspiration on the basis of Bernoulli's physical law. During sleep, the anatomical narrow upper airway will be more prone to collapse. To overcome compromised pharyngeal anatomy, the upper airway dilator muscles of a patient with sleep apnea must be more active during wakefulness than those of healthy controls. Furthermore, increased hypercapnic ventilatory responses could be demonstrated in OSA patients.

Nasal obstruction leads to mouth breathing, which repositions the mandible and causes a tonguebase collapse. Nasal obstruction leads to a resistive preloading of the airway during inspiration, further aggravating the build-up of negative pressure and therefore leads to an increase in arousals and number of apneas (14).

Changing and discoordinated muscle activity is only a predisposing factor for collapse. There is accumulating evidence that collapse occurs at the end of expiration or even during central apneas when inspiration and the corresponding increase in intraluminal negative pressure is not present (15). This means that the intrinsic collapsibility of the upper airway must substantially contribute to the collapse.

The importance of individual variability in ventilatory control mechanisms in the pathogenesis of sleep apnea has been controversial. However, a technique has been developed of proportional assist ventilation to asses loop gain, which is a measure of ventilatory control stability during sleep. Loop gain describes the propensity of a

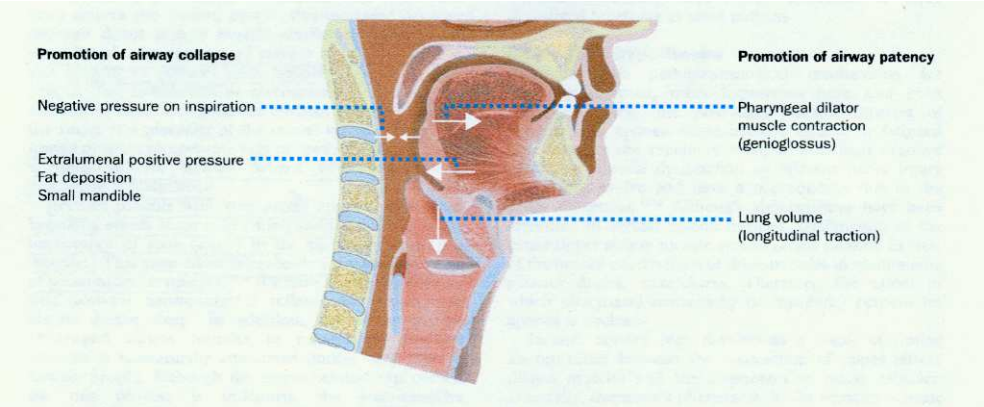
feedback control system to become unstable on the basis of its intrinsic properties (16). For the ventilatory control system, extended circulation time, small lung volumes and high ventilatory drive (responsiveness to hypoxia, hypercapnia or both) tend to destabilize the system and thus increase loop gain. Such results have shown that, independent of upper airway collapse, the loop gain of individuals with obstructive sleep apnea is much higher than that of controls, suggesting that the ventilatory control system in patients with sleep apnea during sleep is intrinsically less stable.

Two models of the upper airway in OSAS are described: collapse occurs as a result of the balance of forces in the UA, and the upper airway as a Starling resistor.

Balance of forces

Although most mammals have rigid skeletal support of the pharyngeal airway, patency of the human upper airway is maintained mostly by muscle activation and soft tissue structures (17). The evolution of speech is thought to have needed substantial laryngeal motility, leading to a hyoid bone without rigid support and a vulnerable airway. Variables tending to promote pharyngeal collapse include negative pressure within the airway (during inspiration) and positive pressure outside the airway (fat deposition, small mandible). Conversely, patency is preserved by activation of the pharyngeal dilator muscles (genioglossus) and by increases in lung volume, which tend to keep the airway open by longitudinal traction (18). As a result, dilating forces (muscle activation) have a complex interaction with collapsing forces (anatomy, airway negative pressure)(figure 1).

Figure 1. Balance of forces model

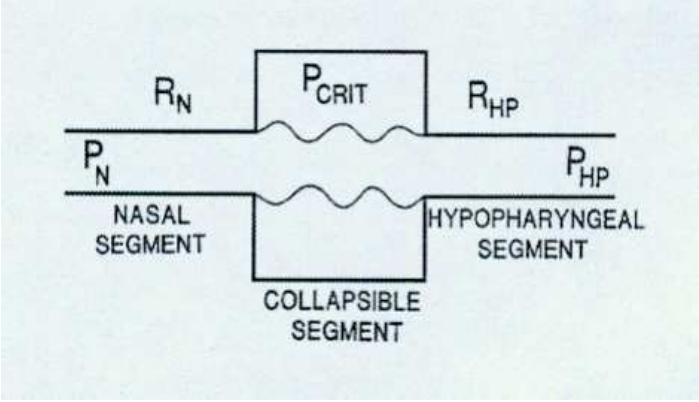


Because of the physiological importance of maintaining pharyngeal patency and the many tasks of this portion of the airway (speech, swallowing, etc), a sophisticated motor control system has evolved, with more than 20 upper airway muscles playing part. The hypoglossal motor system in the medulla, which controls efferent traffic to the genioglossus muscle is affected by cortical events, respiratory pattern generating neurons, peripheral and central chemoreceptors (PaO_2, $PaCO_2$) and input from local mechanoreceptors present in the upper airway itself (19).

Starling resistor

In the Starling resistor model, the upper airway is represented as a rigid tube with a collapsible segment. Upstream (nasal) and downstream (hypopharyngeal) segments have fixed diameters and resistances. The collapsible segment has no resistance but is affected by a surrounding pressure, the critical closing pressure. Collapse occurs only when surrounding pressure exceeds intraluminal pressure. Inspiratory flow will be maintained as long as nasal pressure remains above the critical closing pressure. As a consequence, critical closing pressure is a product rather of the pressure upstream to the collapsible segment than of the hypopharyngeal segment (20). There is a good correlation between critical closing pressure and the clinical picture: Pcrit normals< Pcrit snorers < Pcrit hypopnea patients < apnea patients.

Figure 2. Starling resistor model



5. Diagnostic work-up.

Medical history

Assessment of patients starts with medical history taking with special emphasis on snoring, daytime sleepiness and witnessed apneas.

Snoring can be easily documented using a visual analogue scale (VAS). In this scale the bedpartner of the patient has to quantify the patient's snoring on a scale ranging from 0 (no snoring) to 10 (extreme loud snoring, partner has to leave the bedroom).

There are several tools for the assessment of sleepiness but none of them is considered the gold standard. The Epworth Sleepiness Scale (ESS)(21) is a simple, self-administered questionnaire providing a measurement of the patient's general level of daytime sleepiness, which is a measure of the probability of falling asleep in a variety of day life situations. Use of the ESS is quick, inexpensive, easy and the questionnaire has a high test-retest reliability. An ESS score ≥ 10/24 defines the presence of excessive daytime sleepiness (EDS).

Furthermore, questions about sleep quality, sleep position, nocturnal nasal obstruction, use of medication and alcohol consumption should be included.

Anthropometric data including age, height and weight are mandatory in the work-up of OSAS. Recent change in body weight should be checked.

The medical history in general, and the ESS in particular, do not have a reliable predictive value to exclude OSAS (22).

Clinical examination

The general clinical examination includes measurement of height, weight and neck circumference. A clinical ear-nose-throat examination should be performed with special attention to the pharyngeal dimensions. Tonsil size is graded following Friedman (figure 3)(23). Grade 0 means no tonsils left and grade 4 means kissing tonsils. The modified Mallampati score by Friedman (figure 4) is a measure of tongue size and length of the soft palate. It is a predictive indicator for upper airway surgery outcome in OSAS patients.

Figure 3. Tonsil size score

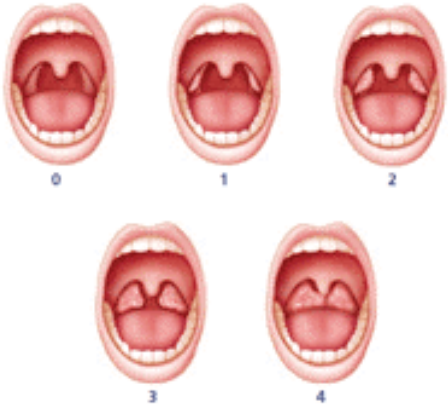
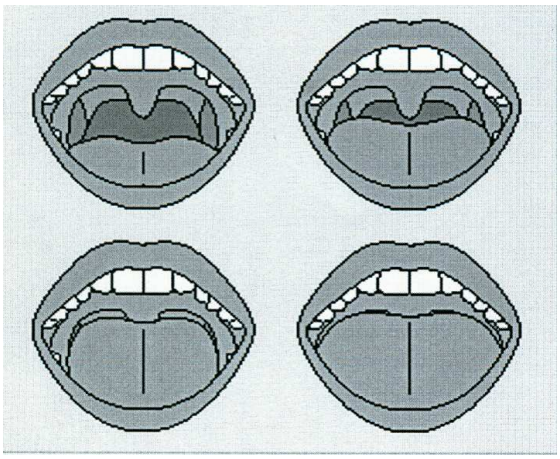


Figure 4. Modified Mallampati score



The length of the uvula and the amount of pharyngeal webbing is evaluated. Anterior rhinoscopy and nasal endoscopy evaluates for nasal pathology. The Müller manoeuvre assesses the pattern of upper airway narrowing in the awake state. The predictive value of this manoeuvre is poor (24). Dental condition is evaluated in case treatment with an oral appliance is considered.

Sleep registration

Sleep apnea can be suspected on the basis of the medical history and the physical examination, but overnight polysomnography (PSG) remains the gold standard in the diagnosis of OSA (25). PSG incorporates recording of electroencephalography (EEG), electro-oculography, snoring (microphone), nasal airflow (canulla),

electrocardiography (ECG), pulse oximetry, tibialis anterior electromyography and inductance plethysmography (respiratory effort).

Unfortunately, PSG is time consuming, expensive and requires highly trained medical staff and appropriate equipment. As a result of growing awareness of OSAS and the limited amount of sleep centers, the need for PSG has increased over the years (26). Therefore the access to PSG might be compromised. Many home diagnostic methods have been investigated with most simply measuring respiratory signals. The current systems vary substantially from two-channel (snoring and oximetry) to four-channel (oximetry, airflow, effort and position), to full polysomnography. In general, the diagnostic accuracy of such tests is about 80%, with increasing channels improving accuracy, but adding complexity (27). However, the role and use of such devices is under investigation.

Specific investigation of the upper airway

Various sites along the upper airway are prone to collapse during sleep. Moreover, UA collapse can occur simultaneously at multiple sites (28). Localization of the pharyngeal collapse in the individual OSAS patient may be important to optimise the results of local treatment.

Various methods are available to determine the site of upper airway obstruction during sleep in OSAS patients. These methods include both static and dynamic methods, performed during wakefulness or sleep. All of them have their specific limitations and advantages (29).

A routine ENT examination of the awake patient in a sitting position, including the Müller manoeuver gives limited information on the upper airway behaviour during sleep. Dimensions of the upper airway change during sleep because of muscle relaxation.

Therefore the examination of the upper airway can be complemented with a dynamic evaluation to determine the site and pattern of upper airway collapse during sleep.

Cephalometry and computed tomography can be performed during sleep (30) but they are static and unphysiological methods which are further limited by their side effects of irradiation. Magnetic resonance imaging may bypass the problem of irradiation, and

ultra-fast sequencing may even provide dynamic study (31), but this method is entirely limited by costs and availability.

Several authors have used multi-sensor pressure catheters positioned in the UA to determine the site of collapse (32). One of the main advantages of this technique is that it can be applied simultaneously during a full overnight PSG. However, conflicting results have been reported when comparing pressure-recordings with flextube reflectometry for the localisation of the site of obstruction (33).

The ideal method would involve direct visualisation of the upper airway during natural sleep. Fiberoptic evaluation of the upper airway during natural sleep was described in the late seventies (34), but this is clearly limited by its requirement for an unnatural sleep laboratory environment, not to mention an unusually compliant sleeping patient. So, the next best option would appear to be drug-induced sleependoscopy.

Sleependoscopy was pioneered by Croft and Pringle in the early nineties (35). They proposed a grading system for upper airway collapse in patients with OSAS. This grading system defines the type and site of upper airway collapse in a specific patient, which may improve patient selection for site-specific treatments (36) .

Sleep endoscopy is currently an integrated part of upper airway evaluation in OSAS patients who are considered for surgery in the guidelines of the Dutch Society of Pulmonology (www.cbo.nl).

6. Treatment of obstructive sleep apnea

Continuous positive airway pressure

OSAS is widely accepted to be associated with high rates of morbidity and mortality, mostly due to cardiovascular disease and traffic accidents (37).

Nasal continuous positive airway pressure (CPAP) treatment remains the treatment of choice for OSAS because its effectiveness in elimination of apnea and improvements in apnea sequelae (38). Results of randomised trials have shown substantial improvements in both sleepiness and neurocognitive performance of patients on nasal CPAP compared with those on placebo or subtherapeutic CPAP (39). However, most of these studies have potential limitations including suboptimal compliance rates (3 - 4.5 h/night)(40), moderate dropout rates (8 – 33%)(41), and the use of different treatment comparisons (placebo pill, conservative management advice)(42).

In a large observational study, in which multivariate analysis adjusted for potential confounders, it was shown that untreated severe OSAS significantly increased the risk of fatal (odds ratio 2.87) and non-fatal (odds ratio 3.17) cardiovascular events compared with healthy participants (43). CPAP treatment significantly reduced this risk, almost to the level of healthy subjects.

Thus, treatment of OSAS should include a trial of CPAP in most cases.

Objective measures of patterns of CPAP use show that a substantial group of patients have difficulties with adherence to the treatment or do not tolerate it at all (44). CPAP was used on an average of 66% of the nights. When CPAP was used, the mean duration of use was 4.9 hours. Although the majority of patients (60%) claimed to use CPAP nightly, only 46 % met the criteria for regular use, defined by at least 4 h of CPAP administered on 70% of the nights monitored. The best compliance was seen in patients with severe OSAS and substantial sleepiness. Strategies including heated humidification or nasal decongestants, steroids or both to alleviate nasal symptoms plus intensive support with regular follow-up improve CPAP adherence (45).

Newer positive pressure devices have gained popularity and include bilevel positive airway pressure machines (different inspiratory and expiratory pressure) and auto-titrating devices, which provide variable pressure levels based on snoring and flow

limitation. Results of clinical trials do not support the use of BiPAP over CPAP, since patient adherence is generally similar (46). However, patients needing high CPAP pressures to eliminate disordered breathing events who complain about the expiratory work of breathing often prefer bilevel positive airway pressure. Results of studies assessing autotitration devices have shown improved adherence in only a few trials, with most finding little effect. Routine use of such devices is difficult to justify because of their increased costs (47).

Oral appliances

There are three categories of oral appliances:

1. soft palate lifters which reduce vibration of the soft palate.
2. tongue retaining devices which hold the tongue forward during sleep in an anterior bilb by suction.
3. mandibular advancement devices (MAD)(figure 5).

Figure 5. Mandibular advancement device

Oral appliances should be considered for patients who have failed or refused CPAP treatment, for those with snoring or mild obstructive sleep apnea and for those who do not respond to surgery (48).

Mandibular advancement devices are the most widespread and evaluated oral appliances. They are worn intra-orally at night to advance the lower jaw and reduce collapsibility of the UA significantly (49). The widening of the pharyngeal cross-sectional area induced by MADs occurs at the level of velo-, oro- and hypopharynx. Both the reduction in UA collapsibility and the widening of cross-sectional area caused by MADs have been reported to be dose-dependent (50).

Randomised cross-over trials comparing MADs with CPAP indicate that MADs reduce the AHI to a lesser or a similar extend then CPAP, nevertheless, MADs appear to have higher compliance rates and a higher patients' preference with fewer side effects and greater satisfaction (48). Custom-made devices turn out to be more effective than thermoplastic devices in the treatment of OSA (51).

The use of MADs might cause side effects: hypersalivation, morning discomfort and pain at the temperomandibular joint are mostly temporally.

Surgical treatment

General principles

The recommendations formulated by the American Academy of Sleep Medicine are as follows (52): surgical treatment is indicated in patients who have an underlying, specific surgically correctable, abnormality that is causing the sleep apnea, or in patients for whom other non-invasive treatments have been unsuccesfull or have been rejected, who desire surgery and who are medically stable enough to undergo the procedure. Furthermore, there is a role for surgery for patients with non-apneic snoring and in patients with mild OSAS. In these patients, conservative measures should be emphasised, including maintenance of nasal patency, avoidance of depressants including alcohol, and the goal of 7-8 hours of sleep per night. In addition, patients with documented positional apnea should be encouraged not to sleep on their back.

Surgical candidates are selected after a proper diagnostic work-up, based upon history, general clinical examination, examination of the UA to determine the site of UA obstruction and polysomnography. Patient-related factors are equally important: age, obesity, comorbodities, previous treatments, functional level and preference of the patient.

Difficulties with the interpretation of surgical results for OSAS arise from the variability in the definitions of surgical success and the lack of proper outcome measures that not only include the apnea severity, in terms of respiratory disturbance index (RDI), but also the long-term effect on quality of life and associated morbidity.

A reduction of the AHI by at least 50% and a postoperative AHI < 20 or a reduction of the apnea index (AI) by at least 50% and a postoperative AI < 10 were proposed as criteria for success in the meta-analysis on UA surgery performed by Sher et al (53). Although these criteria are frequently employed in the current literature on OSAS surgery, their validity might be questioned since recent data show that even mild OSAS can result in cardiovascular morbidity (54). In addition, recent data indicate that polysomnographic date are not consistently associated with daytime sleepiness, quality of life or reaction time in OSAS patients (55). The authors suggested that parameters

other than polysomnographic indices should be considered as outcome measures for treatment to quantify some important aspects of OSAS burden or treatment outcome.
Surgical treatment of OSAS aims to correct anatomical abnormalities in the UA, contributing to its collapse during sleep. The site of UA collapse can be located anywhere between the choanae and the epiglottis. Although overly simplified, the classification system proposed by Fujita et al. to describe the pattern of UA obstruction is still frequently utilised (56). He describes three types of UA collapse: type I is retropalatal collapse, type II is retropalatal and retrolingual collapse and type III is retrolingual collapse. However, investigations into the pattern of UA collapse during sleep indicate that the majority of OSAS patients have a diffuse pattern of UA collapse, most frequently involving both the naso- and oropharynx (57). Only a minority of OSAS patients have a specific space-occupying abnormality in the UA for which surgical removal is corrective. Therefore, the rationale of OSAS surgery has evolved towards a "multilevel surgical concept", dictated by the patient's anatomy. This concept can be realised through a stepwise approach in which a combination of surgical procedures is performed one after the other until a successful result is achieved (58,59).

The UA consists of soft tissues (tonsils, soft palate, uvula, tongue and lateral pharyngeal walls) that are supported by and suspended from the cartilaginous and bony UA skeleton. The special relationship between UA soft tissues is also determined by the orientation of UA muscles with their respective origins and insertions in the craniofacial skeleton. The hyoid bone and the mandible are the most important craniofacial bone structures determining UA size, and individual changes in their shape or position may affect UA patency.

Uvulupalatopharyngoplasty

Uvulopalatopharynoplasty (UPPP) is the most frequently performed surgical procedure for OSAS and snoring. It was introduced by Fujita in 1981 (60). Uvulopalatopharyngoplasty consists of the removal of redundant pharyngeal tissue and

stretching the mucosal folds. This procedure enlarges the oropharyngeal airway through excision of the tonsils, if present, trimming and reorientation of the posterior and anterior tonsillar pillars, and reduction of the uvula and postero-inferior portion of the soft palate (figure 6).

Figure 6. Uvulopalatopharyngoplasty

A review of surgical outcome of UPPP showed an overall success rate of 40.7% according to the definition of surgical success (53). Responders were more likely to have a lower baseline AI or AHI. If patients were selected for palatal obstruction (determined by different techniques during wakefulness or sleep) the success rate was 52.3%. By contrast, among those patients with type II or type III collapse (involving hypopharyngeal obstruction), only 5.3% responded to the surgery. These findings supported the consensus statements of the American Sleep Disorders Association that UPPP, with or without tonsillectomy, may be appropriate for patients with narrowing or collapse in the retropalatal region (61).

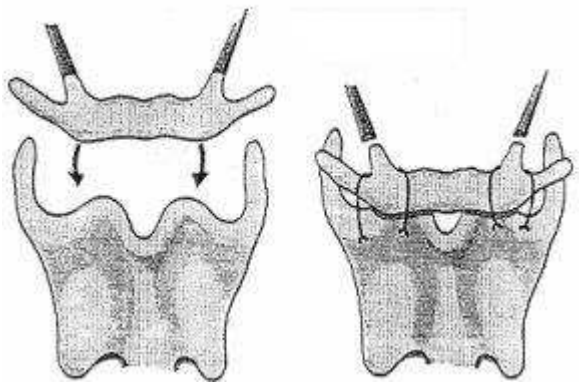
Apparently UPPP has limitations in treating OSAS because most OSAS patients have multilevel obstruction of the UA. Moreover, the present methods for the detection of the site of obstruction are complex, expensive, time consuming and not always reliable (29). Much higher success rates of UPPP have been reported after selecting patients with sleep endoscopy (58).

Given the limitations of UPPP in the treatment of OSAS, a variety of surgical procedures that address the tonguebase and hypopharynx are described in order to improve success rates of surgery for OSAS.

Hyoid suspension

Hyoid suspension, also called hyoidthyroidpexia, involves stabilisation of the hyoid bone inferiorly by attachment to the superior border of the thyroid cartilage (figure 7). The underlying principle for altering the hyoid is that, anatomically, the hyoid complex is an integral part of the hypopharynx. Anterior movement of the hyoid complex improves the posterior airway space and neutralizes obstruction at the tongue base (62).

Figure 7. Hyoid suspension



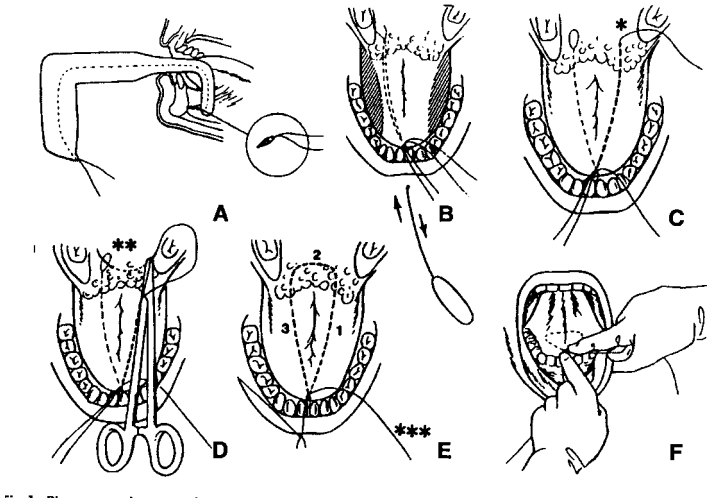
Hyoid suspension is often performed in combination with other UA surgery such as genioglossus advancement or radiofrequency ablation of the tongue base. Hyoid suspension is performed under local or general anaesthesia and has a limited morbidity. Temporal side effects include dysphagia and pain.

A significant decrease in AHI and ESS was reported in several studies (63,64). Limited improvement of snoring was reported. All studies reporting on results of hyoid suspension included patients with severe OSAS and who had palatal surgery before. Surgical success varied from 17% (study population with BMI=34) to 78 % (BMI=29). Significant improvement of EDS was reported in all but one study (65). All studies have level 4 in evidence based medicine (66).

Tongue suspension

The tongue suspension suture technique was first described in 2000 (67). The technique describes the incisionless placement of a bone screw into the lingual cortex of the mandibular symphysis (figure 8). An attached suture of proline is then looped into the posterior tongue base and tied anteriorly. When tightened, the suture supports the anterior hypopharyngeal airway and tongue base, theoretically preventing obstruction.

Figure 8. Tongue suspension suture technique



This technique has the advantage of being nonexcisional, potentially reversible and minimal invasive.

The study of Woodson et al report on feasibility and efficacy in 39 patients (68). Important direct postoperative morbidity including severe pain, severe dysphagia and dysarthria are reported. In 18% of patients, complications including delayed infection, dehydration, sialadenitis and postoperative bleeding, occurred. The mean AHI improved from 33.2 to 17.9 after 2 months follow-up. Limited to no improvement in snoring was observed.

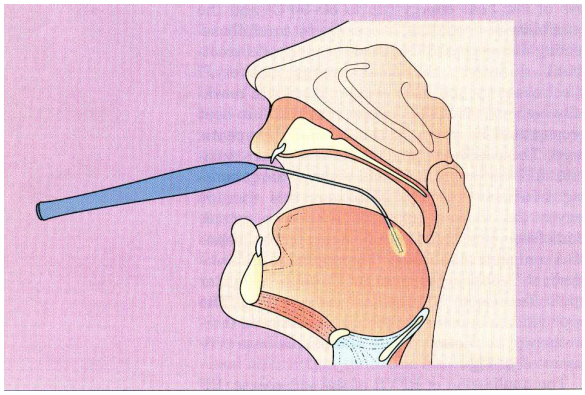
Most studies reporting on results of this procedure include obese patients with moderate to severe OSA. Each study demonstrated an improvement in AHI and the proportion of patients with a successful outcome varied from 20% to 57% (65).

The fact that the advancement of the tongue is not titratable is a clear disadvantage. With this technique, once the knot forming the suspension suture is tied, no more modifications to the advancement of the tongue can be made. Thus, the surgeon has to correctly judge the amount of advancement during the procedure. Because the procedure is performed under general anaesthesia with intubation, complete relaxation of the tongue may hinder a correct judgement of the amount of advancement necessary for a particular patient.

Radiofrequency interstitial thermotherapy of the tongue base

Although the soft palate is the origin of snoring sounds in the majority of patients (69), the tongue base seem to be involved in 15 to 25% of cases (70). Patients without typical findings at the soft palate and with clinical signs of tonguebase obstruction may benefit from tonguebase surgery. Furthermore, tonguebase surgery may be a part of a multi-level surgical approach in patients with multilelel obstruction of the UA (71).

Figure 5. Radiofrequency interstitial thermotherapy of the tongue base



Radiofrequency surgery of the tongue base is simple, minimal invasive and can be performed under local or general anaesthesia under prophylactic antibiotic treatment.
Many studies report on outcome measures for RF of the tonguebase (65). Most reports include overweight and obese patients with moderate to severe OSAS. Most of the studies reported a significant improvement in the AHI, and the success rates ranged from 20% to 83%.

Although the clinical outcome depends on the amount of lesions applied and the total amount of energy delivered, significant reduction of snoring has been reported after RF surgery of the tonguebase in OSA patients (72). Side effects include post-operative pain, dysphagia, swelling of the tongue and increased snoring, but only last for several days.

RF surgery offers the advantage of treating multiple levels of the UA including inferior turbinates, soft palate and tonguebase. In addition, RF treatment can be repeated over time with minimal morbidity to titrate the effect for the patient. The combined use of RF surgery of both the palate and the tonguebase in patients with OSA is safe and effective for both objective and subjective outcome measures (71). A randomised controlled study comparing multilevel RF and CPAP in patients with mild to moderate OSA showed that both treatments were equally effective at improving levels of daytime sleepiness, sleep related quality of life and global quality of life (73).

Multilevel surgery for OSAS

Surgery for moderate to severe OSAS is not a substitute for CPAP, but rather a salvage procedure for those who failed CPAP and other conservative treatments and therefore have no other options. The goal of surgical intervention is to reduce the number and severity of respiratory events when complete elimination of these events is not possible.

As it is clear that most OSAS patients have multilevel obstruction of the UA, the appropriate surgical procedure should be multilevel. In a recent meta-analysis on multilevel surgery (= two or more procedures on 2 or more different levels) in general showed a weighted average improvement of 60% in AHI, 44% increase in %REM sleep, 65% decrease in bedpartner's snoring VAS and 9% increase in quality of life (74).

The results of multilevel surgery were significantly better in patients with severe OSA than in patients with mild to moderate OSAS. The complication rate was 15%. The evidence based medicine (EBM) level of the 49 included papers revealed that only 1 paper was level 1, two papers were level 3 and 46 papers were level 4 evidence.

Bariatric surgery

Bariatric surgery is regarded as the most effective treatment for morbid obesity (75). The degree of benefit and the rate of morbidity and mortality vary according to the surgical procedure (76). Several studies of surgical weight loss interventions have shown substantial decrease in OSAS severity after weight loss (77). Bariatric surgery should be considered in morbid obese OSAS patients with poor CPAP compliance.

In a recent review, bariatric surgery appears to be a clinically effective and cost-effective intervention for moderately to severely obese patients compared with non-surgical interventions. Uncertainties remain and further research is required to provide detailed data on patient QoL, impact of surgeon experience on outcome, late complications leading to reoperation and duration of comorbidity remission. New research must report on the resolution and/or development of comorbidities such as Type 2 diabetes and hypertension so that the potential benefits of early intervention can be assessed (78).

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Chapter 3

Outcome of sleep endoscopy in obstructive sleep apnea syndrome

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A**bstract**

Objectives

Snoring and obstructive sleep apnea syndrome (OSAS) result from upper airway (UA) collapse during sleep. Sleep endoscopy is a dynamic evaluation of the UA that can be used to determine the site(s) of collapse during respiratory events. This study evaluates the feasibility and outcome of sleep endoscopy in patients with OSA, compares the findings with the literature, and reviews the therapeutic advice given to patients.

Methodology

A retrospective analysis was conducted of the data for 70 OSAS patients in whom UA surgery was considered. Sleep endoscopy was performed after IV administration of midazolam and propofol. The UA was visualised and assessed for the location of UA flutter, narrowing or collapse. Feasibility and safety were evaluated retrospectively. Outcome data were described as type and pattern of flutter and/or collapse. Treatment advice given to the patients was reviewed.

Results

Sleep endoscopy showed monolevel palatal collapse in 31.9%, monolevel tongue/hypopharyngeal collapse in 27.8% and multilevel collapse in 31.9% of patients. In 5.6% of patients, no collapse was found. In all patients except 2, reliable assessment proved possible of the site(s) of obstruction. No side effects were reported.

Conclusion

Sleep endoscopy is feasible and safe in daily practice when sedation is performed by an anaesthesiologist and can be used to locate the site of collapse in the UA. Sleep endoscopy findings in our study sample, as well as in the literature, differ according to the content of the study sample and the method of sedation. Treatment advice may differ from sleep endoscopy findings since other factors such as age and patient preferences need to be considered.

Keywords

snoring – sleep apnoea – upper airway - sleep endoscopy

Introduction

Obstructive sleep apnea (OSAS) is a sleep-related breathing disorder caused by repeated partial or complete collapse of the upper airway (UA). These moments of collapse, which are known as "respiratory events", cause apnoea, hypopnoea, increased upper airway resistance and oxygen desaturation, or a combination of these symptoms.

OSA is thought to affect up to 2% of middle-aged women and 4% of middle-aged men[1].

According to the American Academy of Sleep Medicine, OSAS is defined as 5 or more respiratory events per hour (apnoea-hypopnoea-index AHI) accompanied by daytime symptoms[2]. These events lead to recurrent arousals, which in turn result in daytime symptoms like hypersomnolence and fatigue, concentration impairment and an increased incidence of traffic and occupational accidents[3].

Continuous positive airway pressure (CPAP) is the standard treatment for patients with moderate and severe OSAS (AHI>15). However, UA surgery may be considered in subjects with mild disease (AHI < 15) and those who do not tolerate or do not comply with CPAP[4]. In Belgium, CPAP is reimbursed by the health insurance system for patients with an AHI ≥ 20 and an arousal index ≥ 30.

Uvulopalatopharyngoplasty (UPPP) is probably the most widely performed procedure for patients with snoring and OSAS. In a meta-analysis by Sher et al., the overall success rate for this procedure was 41%. This percentage was even lower in patients with multilevel collapse[5]. It is likely that an important reason for this disappointing success rate is inadequate patient selection, and the low success rate suggests that good diagnostic topical work-up to localise the site(s) of obstruction is mandatory to improve treatment results[6].

Many OSAS patients were found to have UA collapse at several sites and a combination of more or less distinct anatomical abnormalities referred to as "disproportionate anatomy". A thorough UA evaluation should therefore precede

therapeutical decision-making for these patients, especially when UA surgery or treatment with a mandibular advancement device is being considered[7].

Various methods are available to determine the site of upper airway obstruction during sleep in OSAS patients. These methods include both static and dynamic methods when the patient is awake or asleep. They all have their specific limitations and advantages[8].
A routine ENT examination of the patient, awake in a sitting position, including the Müller manoeuver[9], supplies limited information about upper airway behaviour during sleep. The dimensions of the upper airway change during sleep because of muscle relaxation.
The examination of the upper airway can therefore be complemented with a dynamic evaluation to determine the site and pattern of upper airway collapse.
Croft and Pringle pioneered sleep endoscopy in the early nineties[10]. They proposed a grading system for upper airway collapse in patients with OSA. This grading system defines the type and site of upper airway collapse in a specific patient, and may improve patient selection for site-specific treatments[11].
Sleep endoscopy is currently an integrated part of upper airway evaluation in OSA patients who are being considered for surgery according to the guidelines of the Dutch Society of Pulmonology (not published).

The attraction of sleep endoscopy is its potential to provide a dynamic visualisation of the anatomical areas responsible for the generation of noise (snoring) or obstruction under conditions that mimic natural sleep. It has been criticised for not being a true reflection of normal physiological sleep and, in some studies, even non-snoring patients started snoring during drug-induced sleep[12]. On the other hand, sleep endoscopy is a simple and non-invasive way of investigating the upper airway during sleep. Sleep endoscopy using target controlled infusion (TCI) of propofol has been validated and it distinguishes between symptomatic and non-symptomatic subjects[13].

The primary purpose of this retrospective study is to evaluate the feasibility of drug-induced sleep endoscopy in patients with snoring and obstructive sleep apnea.
The second purpose is to evaluate the outcome of sleep endoscopy and to compare the findings for our study sample with other samples from the literature.
The third purpose is to compare the sleep endoscopy findings and the therapeutic advice given to the patients.

Materials and methods

Between March 2005 and August 2006, 70 patients who were being considered for UA surgery underwent sleep endoscopy in order to determine the site(s) of collapse. All of these patients presented with a history of snoring and/or excessive daytime sleepiness. The data of these patients were retrospectively analysed. Table 1 lists the patient characteristics, polysomnographic data and subjective scoring of snoring and daytime sleepiness.

Table 1

Subject Demographics

	n	mean (SD)	range
BMI (kg/m²)	70	26.4 (3.28)	19.7 - 33.6
AHI	70	18.5 (12.6)	0 - 73
AHI supine	47	40.5 (27.5)	1 - 98
AHI side	47	10.7 (12.3)	0 - 62
VAS snoring (/10)	64	7.5 (2.8)	0 - 10
ESS	68	9.9 (5.4)	1 - 21
Age (years)	70	49.3 (8.4)	26 - 78

BMI=body mass index,AHI=apneahypopnea index, VAS=visual analogue scale, ESS=epworth sleepiness scale

At the first visit and after a routine ENT examination, all the patients with a history of snoring and/or excessive daytime sleepiness were scheduled for polysomnography. In all these patients, the severity of snoring was assessed with a 10-point, bed-partner-evaluated, visual analogue scale (VAS) ranging from 0 (no snoring) to 10 (extreme snoring where bed partner has to leave the room). Daytime sleepiness was assessed using the Epworth Sleepiness Score (ESS). It ranges from 0–24, and abnormal somnolence is considered to be represented by a value greater than 10 [14].

At the second visit, polysomnographic data and therapeutical options were discussed with the patient. Only those patients with mild OSA (5<AHI<20), who did not meet the criteria for CPAP reimbursement in Belgium, were scheduled for sleep endoscopy to locate the site(s) of obstruction. Patients with moderate to severe OSA (AHI>20) were scheduled for CPAP titration. Patients with non-apnoeic snoring did not undergo sleep endoscopy since palatal flutter is the most likely cause in these patients[15]. Local palatal treatment was proposed as the first-step treatment. Patients with CPAP intolerance or poor compliance were also scheduled for sleep endoscopy, regardless of the AHI.

Patients scheduled for sleep endoscopy were evaluated for risk factors by the anaesthesiologist[16]. Table 2 shows the inclusion and exclusion criteria. These criteria apply to patients who undergo sleep endoscopy without the involvement of an anaesthesiologist. In those cases where sedation is performed by an anaesthesiologist, patients with AHI>40 may be included.

Table 2

Inclusion and exclusion criteria for sleep endoscopy[16]

1. Inclusion criteria for sleep endoscopy:
   - AHI < 40 or AI < 30
   - ASA classification I and II
   - Invasive intervention or surgery is considered
   - CPAP intolerance
2. Absolute exclusion criteria for sleep endoscopy:
   - AHI > 40 or AI > 30
   - ASA classification > II
   - Conservative management is preferable (weight loss, positional therapy, NCPAP,…)
3. Relative exclusion criteria for sleep endoscopy:
   - Severe obesity
   - Alcohol abuse

The patients were hospitalised in the surgical day care centre. Sleep endoscopy was performed in a darkened operating room with the patients in a supine position. To mimic the sleep condition of the patient at home, the patient was positioned in a hospital bed instead of on the OR table. Continuous monitoring took place with electrocardioagram and oxygen saturation. An anaesthesiologist induced artificial sleep through the intravenous administration of midazolam and propofol. Midazolam was administered in a bolus injection (1.5 mg) and propofol was titrated by target controlled infusion (TCI). No local anaesthetic was used in the nose in order not to interfere with the effect of local reflexes on breathing[17]. Before the state of unconsciousness was achieved and the patients started snoring, a flexible videolaryngoscope was introduced through the nose to visualise the upper airway and to assess the location of upper airway narrowing or collapse.

After the introduction of the flexible endoscope, it took a few minutes to reach a stage of stable sleep where reliable assessment was possible of the pattern and site of obstruction. Once the endoscope was introduced, the manipulation of the endoscope was kept to a minimum in order not to wake up the patient since this could cause irritation in the nose or throat, resulting in bothersome sneezing.
After sleep endoscopy all patients were moved to an upright position and an oxygen mask was placed on the nose. The patients were monitored in the recovery room for 1 hour. Three hours after sleep endoscopy, patients were discharged. All of them were told to leave the hospital with a companion, and not to drive a car. Patients were given a new appointment to discuss the results of the sleep endoscopy. Discussion of the results directly after the procedure was not recommended because most patients experience retrograde amnesia due to the sedation.

Obstruction was specified as flutter or collapse. Collapse was specified as monolevel palatal collapse (type I), multilevel palatal and tonguebase (type II) or monolevel tonguebase collapse (type III) in accordance with Fujita[18]. The type of collapse was described as circular, postero-anterior or originating from the lateral wall. Flutter was described as present or absent, and the site was noted.

Data relating to the therapeutic advice given after sleep endoscopy were reviewed.

Results

Sleep endoscopy was easily performed in all patients. It took about 20 minutes per patient, including the induction of sedation and transport to the recovery room.
There was no severe O_2 desaturation during the procedure. When saturation dropped below 85%, a chin-lift manoeuvre was performed to open the upper airway. In all cases this manoeuvre resulted in an immediate improvement in oxygen saturation. No intubation (emergency or otherwise) was needed in this group of patients.

The reliability of sleep endoscopy was poor because of bothersome continuous sneezing in 2 cases (2.8%). Visibility was sometimes compromised by abundant saliva but this could be removed in all cases with a small suction probe through the nose, resulting in good visibility. No other side-effects were noted.

Tables 3, 4 and 5 set out the endoscopic findings.
Table 3 shows the type of collapse. Monolevel obstruction (type I and type III) was observed in 61.4% of patients, while multilevel obstruction (type II) was found in 32.9%. No obstruction was observed in 5.7% of patients.

Table 3

Type of collapse (N=70)

No obstruction	Monolevel obstruction			Multilevel obstruction
	Palate Type I	Tongue/Hypopharynx Type III	Total	Type II
4 (5,7%)	23 (32.9%)	20 (28.5%)	43 (61.4%)	23 (32.9%)

Table 4 specifies the pattern of collapse. Palatal collapse was mainly described as a circular collapse (58.7%). Lateral wall or antero-posterior collapse was of minor importance at the palatal level. The same tendency was seen at the hypopharyngeal level: circular collapse was seen in 46.5%. The generation of a snoring sound (flutter) (table 5) was mainly observed at the palatal level (69%). Flutter was observed at the hypopharyngeal level in only 20% of cases.

Table 4 Pattern of collapse according to obstruction site			
	anteroposterior	laterolateral	circular
Palatal	9 (19,6%)	10 (21,7%)	27 (58,7%)
Tongue / Hypopharyngeal	14 (32,6%)	9 (20,9%)	20 (46,5%)

Table 5 Generation of noise: site of flutter (N=70)			
Absent	Palatal	Tongue/Hypopharyngeal	Multilevel
6	49	13	2

After sleep endoscopy, patients were given treatment advice (Table 6) based on the severity of OSAS, the results of the ENT examination, age, findings based on sleep endoscopy and patient preference. This table mentions two experimental surgical treatments: hyoid-expansion[19] and adjustable tongue advancement[20]. Both surgical procedures address the hypopharyngeal segment of the UA.

Table 6 Endoscopic findings and therapeutic advice (n=70)				
Collapse	Absent	Palatal	Tongue/Hypopharyngeal	Both sites
Therapeutic advice				
No therapy	0	2	0	0
MAD	1	0	8	9
UPPP	3	13	4	9
RF Palate	0	1	0	0
RF Tongue	0	0	1	1
RF palate and tongue	0	0	1	1
Hyoid expansion	0	6	2	1
Advance	0	1	4	1
CPAP	0	0	0	1
Total	4	23	20	23

Discussion

In our experience, sleep endoscopy proved to be a convenient and safe way of assessing upper airway obstruction in OSA patients. The procedure was well tolerated by all patients. No adverse events were seen, and the level of obstruction and snoring could be located in all but two patients. In 2 cases (2.8%) the reliability of the procedure was poor.

Sleep endoscopy remains controversial. It has been demonstrated that snoring and sleep apnea varies with sleep position and sleep stage[21]. Information about the site of the obstruction is particularly important when surgical therapy is being considered. Although X-ray cephalometry and computed tomography could be performed during sleep, these are static and non-physiological approaches to UA investigation, and are limited by the side-effects of irradiation[22]. Magnetic resonance imaging is a safe method and can be used to perform dynamic studies of the upper airway, but its potential use is limited by costs and availability[23]. The ideal method is the direct visualisation of the upper airway during natural sleep with a flexible endoscope via the nose[24]. This method depends on the sleep quality of the patient while an endoscope is present in the nose and while sleeping in an unnatural sleep laboratory environment. It also places a heavy burden on the sleep laboratory personnel and the physician performing the examination. The next best option appears to be drug-induced sleep endoscopy. However, it remains controversial for several reasons.

Drug-induced sleep endoscopy comes closer to the natural physiological state of sleep than all the other methods currently available. However, the procedure suffers from major limitations.

It is uncertain whether the short analysis time (15-20 minutes) is representative for all obstructive events during a full night of sleep. Since the procedure is performed only in the supine position, it is not possible to evaluate positional effects.

Midazolam may induce excessive muscle relaxation during sleep, yielding false-positive obstructive events. On the other hand, if this is the case, relaxation affects the

entire upper airway and not a specific site. We do not therefore believe that there will be a major effect on the site of obstruction. The use of TCI with propofol, starting at a low target concentration which is slowly increased, provides an objective and reproducible state of sedation, reducing the likelihood of excessive muscle relaxation and consequent false-positive obstructive events, and therefore enhancing the validity of sleep endoscopy[13].

Sleep endoscopy is a subjective assessment. There is probably inter-observer variability and also variation between anaesthesiologists' sedation methods, for which there are no standardised protocols. Sleep endoscopy should therefore be performed by an experienced physician using a strict protocol for both collecting and reporting the data as described above.

If the inclusion and exclusion criteria are respected, sleep endoscopy is a safe procedure. These inclusion criteria are extremely important in those cases where the sedation is performed by a non-anaesthesiologist[16]. Oxygen desaturation due to obstructive events during sedation might be a risk in patients with severe OSA. We perform sleep endoscopy together with an anaesthesiologist, and we are therefore able to perform the procedure in patients with severe OSA. In the case of severe oxygen desaturation, the anaesthesiologist is able to intervene immediately.

In our experience, sleep endoscopy was useful for counselling the patient about the nature of the disease and the need for further treatment (with possible associated morbidity).

Table 7 compares our sleep endoscopy findings with data in similar studies in the literature[11,25, 26].

Table 7

Comparison of results of our sample with literature.

Obstruction:	None	Monolevel			Multilevel
		Palate	Tongue/ Hypopharynx	Total	
Present study (n=70)	4 (5.5%)	23 (31.9%)	20 (27.8%)	43 (59.7%)	23 (31.9%)
Hessel study[26] (n = 340)		74 (21.7%)	8 (2.4%)	82 (24.1%)	205 (60.3%)
Quinn study[25] (n= 50)		35 (70%)	4 (8%)	39 (78%)	11 (22%)
Pringle study[11] (n=70)		33 (47.1%)	9 (13%)	42 (60%)	28 (40%)

In our study, monolevel obstruction was seen in 61.4% of our patients: palatal obstruction in 32.9% and tongue/hypopharyngeal obstruction in 28.5% of cases. Quinn et al.[25] and Pringle et al.[11] report comparable rates of monolevel collapse: 78% and 60% respectively. Hessel et al.[26] report 24.1% for monolevel collapse, which is substantially lower than the rate we found.

Hessel's study included patients with socially disturbing snoring without excessive daytime sleepiness, but with comparable BMI and age. It does not state the mean AHI for the included patients, but since the study adopted stringent inclusion criteria (table 2), they probably included patients with mild disease. We included patients with a mean AHI of 18.5 (range 0-73) and a mean ESS of 9.9. Since the role of the hypopharynx increases with the severity of the disease, this could explain why we found more monolevel hypopharyngeal obstruction (28.5%) than in their sample (2.4%). The fact that they report a very high percentage of multilevel collapse in their

sample (60%) is probably due to the fact that their assessment of upper airway narrowing was less stringent than ours. We would expect a relative low percentage of multilevel collapse in a group of patients with snoring only and without excessive daytime sleepiness. The fact that they use a higher dose of midazolam (7-12 mg) for sedation might explain a more collapsible airway in comparison with propofol. Quinn's study[25] included only non-apneic snoring patients, and did not state the cut-off AHI value. The mean age of their sample was comparable with ours, but they included no data about BMI. Since OSA was excluded from this group of patients, it is logical that they report a 70% rate of monolevel palatal obstruction. Their observation of 22% multilevel collapse seems high for a sample of non-apneic snorers. Their method of sedation (midazolam 12 mg IV and topical nasal anaesthesia) may well explain these findings. The endoscopic findings in Pringle's study[11] are closest to our findings, although that study did not include any demographic or polysomnographic data about their sample. They included both snoring and OSAS patients without defining them. It is therefore impossible to comment about the comparability of the findings.

This study makes it clear that snoring noise is mostly generated by palatal flutter (68%). In 19% of cases it is generated by vibrations of the hypopharyngeal lateral wall or the epiglottis. This finding compares well with the fact that UPPP is an efficient treatment for snoring, although not always efficient for OSA[5].

Treatment advice was given according to the patient complaints, severity of OSA, age and comorbidity, the characteristics of collapse observed during sleep endoscopy and patient preference. In some cases, therefore, advice about treatment could contradict the sleep endoscopy findings. The four patients with no collapse had an AHI in excess of 15, which warranted treatment. Both ENT examination and PSG results were taken into account when deciding to proceed with UPPP in 3 of these patients. The fourth patient opted for a mandibular advancement device himself. Of 23 patients with monolevel palatal collapse, 13 were advised to undergo UPPP. Six patients were advised to undergo hyoid expansion[19] because of the severity of OSA and because of the collapsibility of the hypopharynx seen during the Müller manoeuvre. In 2 cases it

was agreed with the patient not to proceed with treatment because there was no medical reason to treat (despite their snoring) and because of the patients' reluctance to undergo surgery. The 20 patients with monolevel hypopharyngeal/tongue-base collapse were treated with a procedure addressing the hypopharynx in all but 4 patients. These 4 patients were advised to proceed with UPPP because their main complaint was snoring without daytime sleepiness. Eleven of the 23 patients with multilevel collapse were advised to undergo treatment addressing both the palatal and tongue-base levels. UPPP was advised in 9 patients because their major complaint was snoring without daytime sleepiness. Radiofrequency ablation of the palate and/or tongue base was performed at the request of the patients to prevent morbidity.
In 41 patients (58.6%), the treatment advice matched the sleep endoscopy findings.
Sleep endoscopy is not the "final diagnostic tool" upon which the treatment decision is based. It should be considered part of a comprehensive diagnostic work-up taking into account both patient characteristics and habits, UA findings, polysomnographic data and the personal experience of the surgeon.

Conclusion

Drug-induced sleep endoscopy is a fast and safe way of evaluating the site(s) of upper airway obstruction. Sleep endoscopy findings help to choose a targeted treatment. A standardised method for the procedure is essential to minimise inter-observer and inter-anaesthesiologist variability, yielding reproducible results. Treatment advice was given taking into account the sleep endoscopy findings in the majority of the patients but additional patient characteristics were considered to be more important in the final decision-making, and so the advice did not always match the findings. Further analysis of outcome after treatment will assess the value of sleep endoscopy for the selection of surgical techniques and treatments for patients with OSA.

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Chapter 4

Hyoid expansion as a treatment for obstructive sleep apnea: a pilot study

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Abstract

Objectives:

Hyoid expansion is a novel procedure that aims at widening of the hypopharynx in order to improve obstructive sleep apnea.

Study design: prospective, non-randomized multicenter feasibility, safety and efficacy pilot study.

Method:

An implantable device (Air Frame System) was used to surgically expand the hyoid bone in order to stabilize the hypopharyngeal lateral walls.

Results:

The procedure was performed without technical adverse events. Three clinical adverse events occurred. Tolerability was good. No objective improvement of apnea-hypopnea-index was achieved. There was a significant improvement in snoring and excessive daytime sleepiness.

Conclusion:

Based on the presented data, hyoid expansion is not suitable for the treatment of patients with obstructive sleep apnea. Further use of this procedure with the Air-Frame system is not recommended.

Keywords: hyoid, hypopharynx, sleep apnea, tongue base

Introduction

Obstructive sleep apnea syndrome (OSAS) is a sleep related breathing disorder caused by repeated partial or complete collapse of the upper airway (UA). These moments of collapse, called “respiratory events”, cause apnea, hypopnea, increased upper airway resistance and oxygen desaturation, or a combination of these. As a consequence of these events, frequent arousals may occur during sleep resulting in sleep-fragmentation and therefore complaints of hypersomnolence (1) and fatigue, concentration-impairment and increased incidence of traffic accidents (2). Loud snoring is one of the most common complaints for which subjects consult a physician. Subjects with OSA are prone to long-term morbidity and mortality (3,4).
Four percent of men and 2% of women meet the minimal diagnostic criteria for OSA (5). Obesity, a compromised upper airway anatomy, age and post-menopausal status are important risk factors (6).

Surgery for OSAS is indicated in patients who do not tolerate CPAP or in case a surgically correctable upper airway anatomy is present (7).
Innovative research in surgery for OSAS is justified because a) a substantial group of patients do not comply with CPAP because of side-effects, intolerance (8), or lack of substantial benefit (9), b) the poor results of UPPP (10) and c) the present hypopharyngeal procedures are invasive and lack evidence based efficacy (11).

Lateral wall collapse at the hypopharyngeal segment of the UA might play a role in the pathogenesis of OSA (12). The role of the lateral wall in the circumferential collapse pattern of the hypopharynx is observed in OSAS patients undergoing flexible endoscopy of the UA during drug-induced sleep (13).
Substantial increase in airflow and drop in “closing pressure” was observed by performing expansion hyoidplasty in a canine model (14). The hyoid bone is a horseshoe-shape bone surrounding the hypopharynx. This relationship to the hypopharyngeal lateral wall and its easy surgical accessibility makes the hyoid bone a potential ideal substrate to stabilize the UA lateral walls.

The present study evaluates a novel procedure that addresses the hypopharynx. The Air-Frame™ system (Aspire Medical, Sunnyvale, California, USA) is an implantable device which was used to surgically expand the hyoid bone in order to stabilize the hypopharyngeal lateral walls. The purpose of this paper is to describe the procedure, to emphasize the technology and method of implantation and to present the results concerning feasibility, safety and efficacy.

Material and method

Study design

This prospective, nonrandomized, multicenter study evaluated the feasibility, safety and efficacy of the Air-Frame system. The study was performed in the University Hospital Antwerp (Belgium), the University Hospital Mannheim (Germany) and the Saint Lucas Andreas Hospital in Amsterdam (The Netherlands). The study protocol allowed 30 patients to enter the study with a follow-up time of 6 months. Between January and June 2005, 25 patients were included. The protocol was approved by the Ethics Committee of the three institutions. Informed consent was signed by the patients prior to inclusion in the study.

Inclusion and exclusion criteria for this study are summarized in table 1.
All patients included in this study were intolerant to CPAP therapy and showed evidence of lateral wall collapse. Selection for lateral wall collapse was performed by clinical and endoscopical (Müller manoeuvre) examination in the awake patient and/or drug-induced sleep endoscopy (15). Patients' characteristics are shown in table 2.

Table 1. Study criteria

Inclusion criteria

- Documented diagnosis of obstructive sleep apnea with AHI 15-40 measured within 90 days prior to the planned procedure
- Age ≥ 20 and ≤ 60 years old
- Body Mass Index (BMI) ≤ 30
- Signed informed consent to participate in this clinical study
- CPAP intolerance/refusal
- Evidence of lateral wall collapse

Exclusion criteria

- Prior hyoid surgery
- Other airway surgery within 90 days
- Identified obvious palatal stenosis
- Enlarged tonsils
- Significant mandibular deficiency/retrognathia
- Pregnancy
- Enrollment in another pharmacological or medical device study that may effect or bias the results of the study

Table 2. Patients characteristics

	Average	Range	SD
Age	45,0	27-57	8,4
BMI	26,9	23-30	2,4
Male/Female	24/2	n/a	n/a
AHI	25,3	15-49,9	5,6

Implant

The Air-Frame system consists of a two-piece device, to be implanted in the centre of the body of the hyoid bone after it has been split in the midline, and a delivery clamp.

Procedure

The patient is positioned in the supine position with the head extended. The anterior neck region is prepared sterile. Under general anesthesia with oral intubation and antibiotic prophylaxis (2 g cefazolin), a 4 cm horizontal incision is made at the level of the hyoid bone. The body of the hyoid bone is exposed and freed from the insertion of the thyrohyoid membrane. The hyoid bone is split on the midline. On each end of the exposed body of the hyoid bone, a part of the Air Frame system is delivered with the clamp and fixed on the hyoid bone with a screw. The two parts are connected with two additional screws (Figure 1 and 2). An expansion of about 10-11 mm is achieved. A temporary drain is left in place for 2 days. The wound is closed in 2 layers.

Figure 1. Air-Frame system is delivered to the hyoid bone with use of a clamp

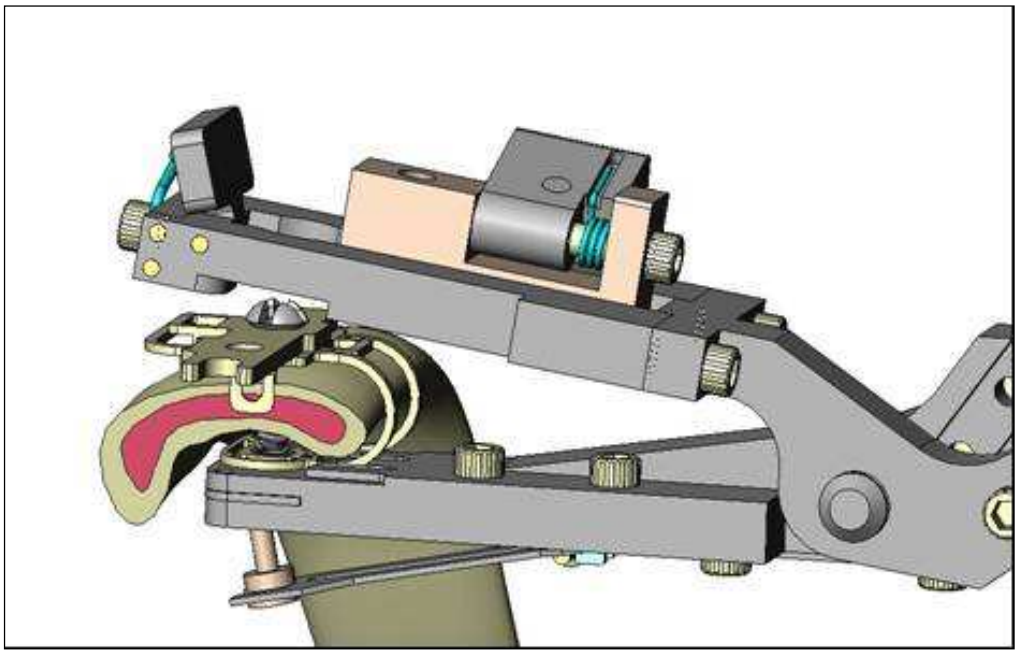
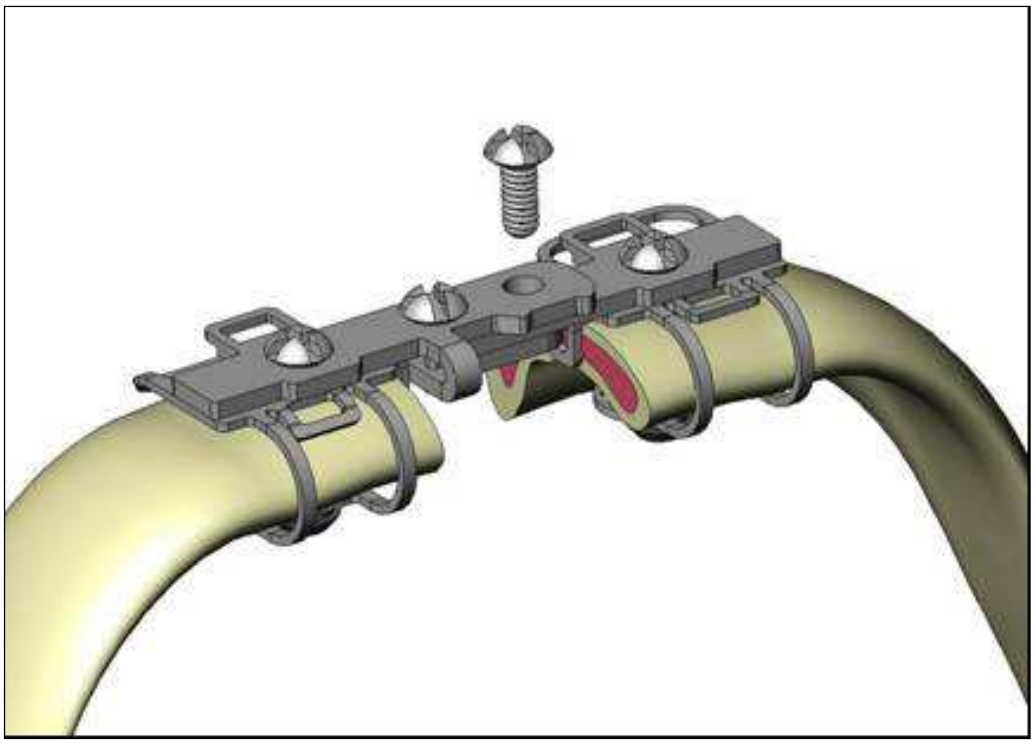


Figure 2. The Air-Frame system is fixed to the body of the hyoid bone with 4 screws



Outcome measures

The objectives of this study were to evaluate feasibility, safety and efficacy of the Air-Frame system. Feasibility of the procedure was evaluated by the procedure time and occurrence of technical adverse events during the procedure. Safety was evaluated by the occurrence of clinical adverse events. Adverse events were defined as the occurrence of any medical event during the study. A serious adverse event was defined as any medical event leading to death, serious deterioration of the health status of the patient or leading to hospitalisation.

Tolerability was assessed with a pain visual analog scale (VAS) ranging from 0 (no pain) to 10 (extreme pain) at baseline and during 5 consecutive days after the procedure. All patients were given pain-killers during the procedure and in the recovery-room, according to the anaesthesiologist's choice.

Efficacy was evaluated by the reduction of AHI, snoring and daytime sleepiness. Standard full-night polysomnography (PSG) was performed for screening and 6

months follow-up. No separate baseline PSG was performed: screening PSG was used as baseline for statistical analysis. Sleep recordings were scored manually in a standard fashion by the same qualified sleep technician, and scoring was blinded for the sleep technician. The AHI was the average number of respiratory events per hour of sleep. Apnea index and lowest oxygen saturation were also evaluated.
Surgical success was defined as a 50% or greater reduction of the AHI and a final AHI of less than 20 (10). Snoring was evaluated with the Snore Outcomes Survey (SOS) ranging from 0 (worst) to 100 (best)(16). Daytime sleepiness was assessed by completing the Epworth Sleepiness Scale (ESS) (17) at baseline and 3 months follow-up. An ESS score above 10 defined excessive daytime sleepiness.

Statistical analysis

All data were stored in and analysed with Microsoft Office Excell 2003 (Microsoft, Redmond, Washington). The results were presented as means, ranges and standard deviations. A paired t-test was used to compare data at baseline and 6 months follow-up for PSG variables and to compare data at baseline and 6 months follow-up for scores of SOS and ESS. A 2-tailed p-value of less than 0.05 was considered statistically significant.

Results

Between January and July 2005, 25 patients were implanted with the Air-Frame system (17 in Antwerp, 7 in Mannheim and 1 in Amsterdam)
All patients completed the 6 months follow-up. There was no significant change in BMI for any of the patients during the study. No patients were lost to follow-up and there were no dropouts. All data of objective and subjective outcome measures were available for statistical analysis.

Feasibility

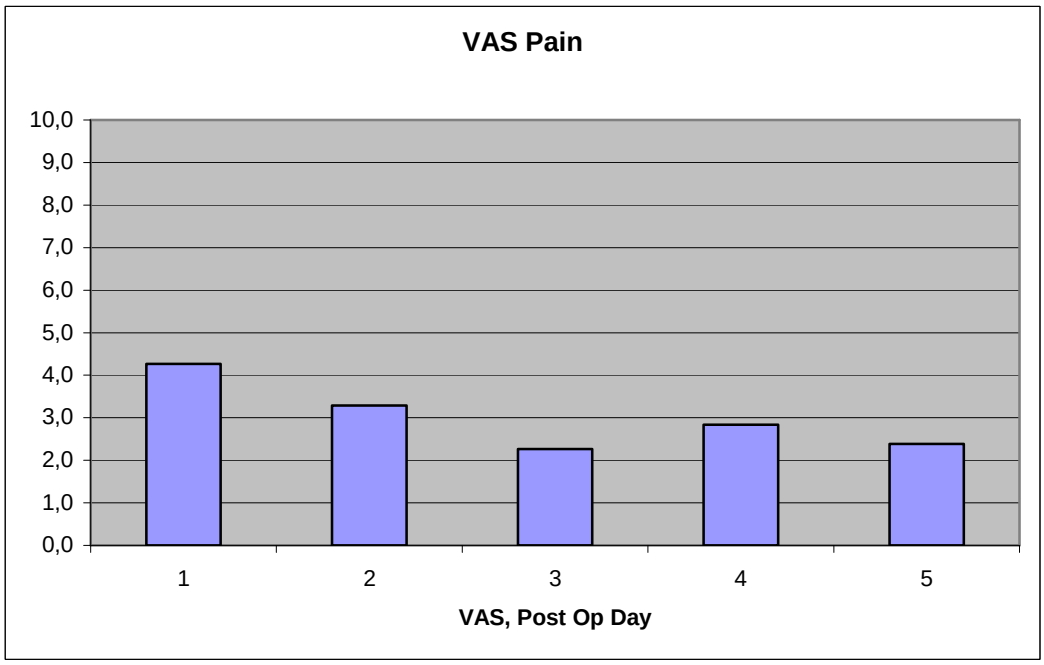
The implantation of the Air Frame system was successfully performed in all cases. During one procedure, the mucosa of the hypopharynx was opened while dissecting the hyoid bone. This was peroperatively closed with a suture. No post-operative leak was noticed.
No technical complications were observed at any of the procedures.
The average procedure time was 68 minutes.

Three adverse events (AE) were noted during the study. One patient reported a common cold 3 weeks after the procedure. This AE was not procedure related nor device related. One patient developed granulation tissue at the wound site. Both conservative therapy with antibiotics and non-steroidal anti-inflammatory drugs and surgical removal of this granulation under local anesthesia were performed and successfully resolved this problem. This AE was probably device related. One patient reported on severe neck pain after the procedure. This was probably due to the positioning of the patient during the procedure with extension of the head. This AE was procedure related, but not device related.
There were no serious adverse events during the 6 months follow-up.

Tolerability

All patients were in good health at any of the follow-up visits and there have been no observations of infection, seroma formation, irritation, hematoma, extrusion or migration of the implant. The patients did not report any lasting foreign body sensation or irritation due to the implant or procedure. None of the patients showed signs of dysphagia or dysphonia during the immediate postoperative period of implantation. Post procedural pain (figure 3) was limited and lasted 1 or 2 days in most patients. None of the patients required narcotics to manage pain.

Figure 3. Postoperative pain score with use of visual analogue scale (VAS)



Objective outcome

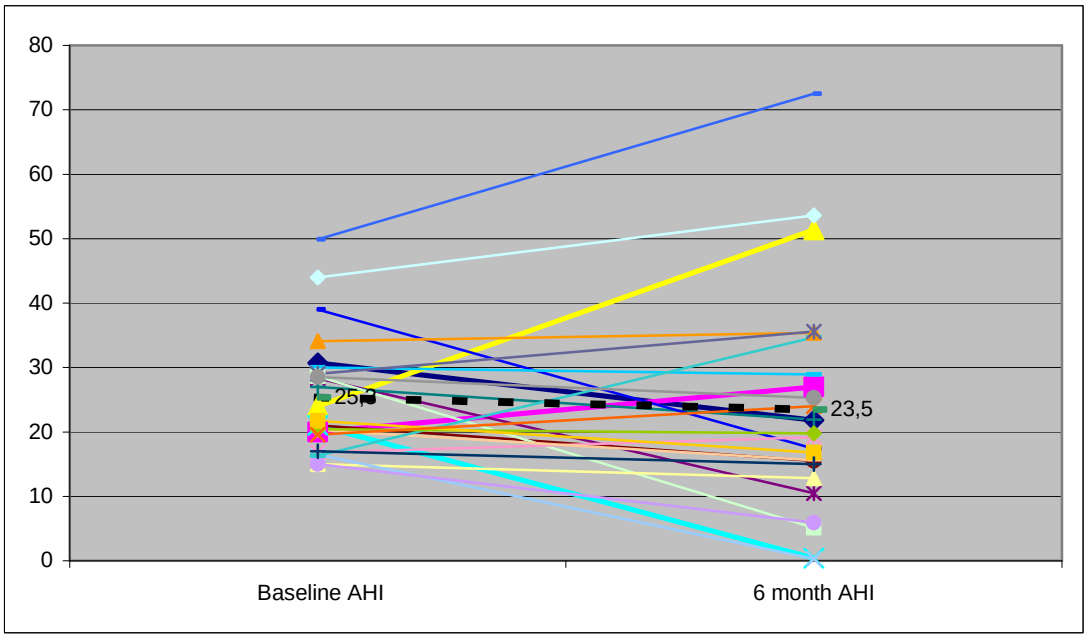
The results of polysomnographic data are presented in table 3.

The average AHI was reduced from 25.3 to 23.5, but this was not statistical significant (p=0.47) (figure 4). There was no statistical change in apnea index (AI) and lowest oxygen saturation (LSAT). Six patients (24%) showed 50% reduction in AHI and 10 patients showed a post-operative AHI below 20. Five patients (20%) showed both a 50% reduction in AHI and a post-operative AHI below 20. Six patients showed a mild increase in post-operative AHI and three patients showed a severe increase in post-operative AHI.

Table 3. Polysomnographic data.

	Baseline			6 month follow up		
Patient ID	**AHI**	**AI**	**LSAT**	**AHI**	**AI**	**LSAT**
A1	20	6,8	77	27	13,3	82,0
A2	24	6,4	67	51,4	10,2	75,0
A3	21	0	75	0,4	0,0	95,0
A4	21	0	85	15,5	0,5	90,0
A5	27	0	86	21,9	4,5	81,0
A6	39	0	66	17,4	2,6	80,0
A7	30	1	79	28,9	2,6	67,0
A8	44	25	70	53,6	4,0	67,0
A9	28,6	1	65	5,1	4,8	81,0
A10	20,3	0	89	15,6	1,0	87,0
A11	49,9	2,6	66	72,5	32,4	73,0
A12	20,4	0	81	19,8	2,3	73,0
A13	21,7	3,2	84	16,8	15,8	84,0
A14	34,1	14,4	81	35,4	22,0	79,0
A15	19,6	6,7	78	24	6,2	79,0
A16	29	15	82	35,6	1,0	81,0
A17	28,5	10,5	81	25,3	0,0	87,0
M1	30,7	1,4	88	21,8	8,5	86,0
M2	28,3	15	85	10,5	0,4	88,0
M3	15	7,2	89	12,8	2,5	87,0
M4	16,5	0,3	90	0,3	0,0	89,0
M5	16,8	0,5	84	19,2	0,4	86,0
M6	15	0,5	86	5,9	4,1	78,0
M7	16,3	0,2	88	34,7	3,8	81,0
N1	17	6	86	15	12,0	83,0
mean	25,3	4,9	80,3	23,5	6,2	81,6

Figure 4. Apnea-hypopnea index measured at baseline and 6 months.



Subjective outcome

The ESS improved from 11.0 at baseline to 7.6 at 6 months follow-up (figure 5) and reached statistical significance (p=0.0004). Eleven patients (44%) did not show an ESS above 10 before treatment. Six patients (24%) had their daytime sleepiness problem resolved.

The SOS score improved from 24.8 at baseline to 59.6 at 6 months follow-up (figure 6), which was statistical significant (p=0.00005).

Figure 5. Epworth Sleepiness Scale measured at baseline and 6 months follow-up. P=0.0004

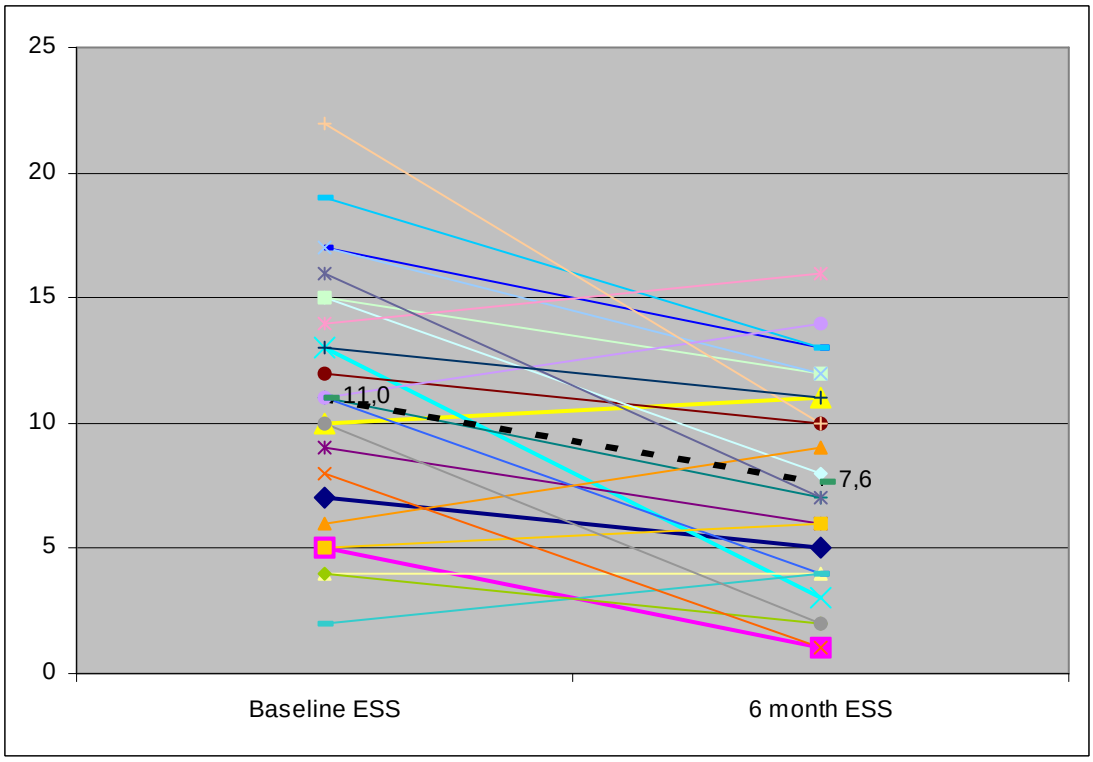
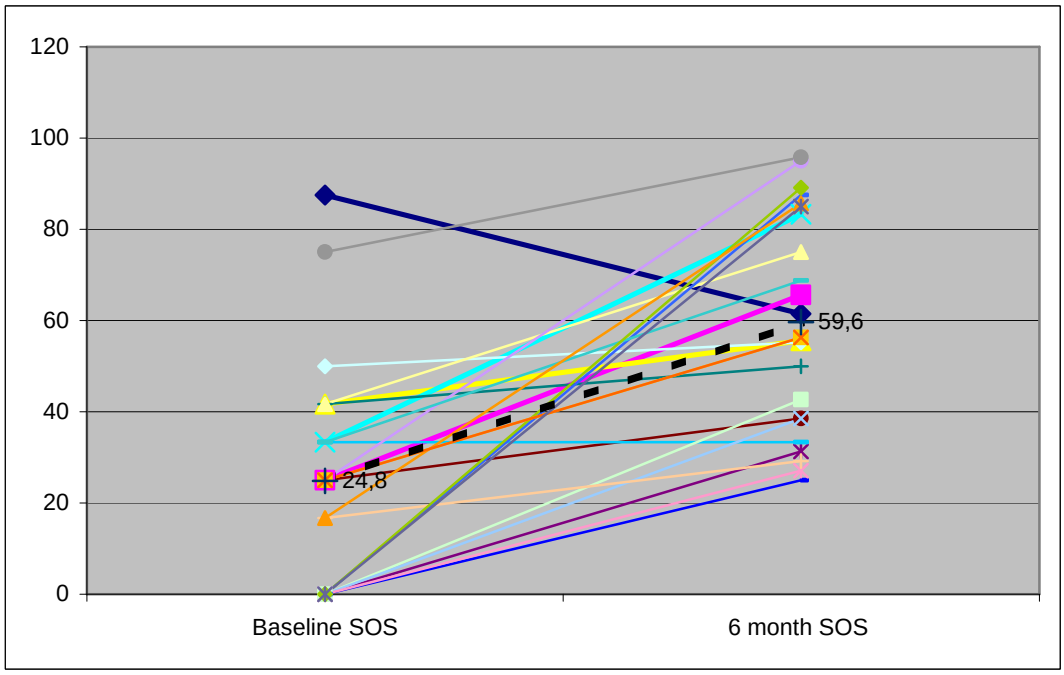


Figure 6. Snore Outcomes Survey (SOS) measured at baseline and 6 months follow-up. P=0.00005



Discussion

This is the first study reporting on hyoid expansion for obstructive sleep apnea in human subjects.

The concept of this procedure was earlier investigated in animals (14), where an increase in flow and a decrease in closing pressure of the UA were reported. Since this is a feasibility pilot study, only a limited sample of selected patients with hypopharyngeal lateral wall collapse was included and only limited conclusions can be stated on efficacy of this procedure.

Hyoid expansion with the Air-Frame system is an novel procedure that aims for expansion of the hypopharyngeal airway space by tensioning the hypopharyngeal lateral walls in the lateral direction. The idea of stabilizing the lateral walls originates in creating extrinsic lateral traction on the lateral walls by pushing the 2 corns of the

hyoid bone outwards. This study is not evaluating the effect of hyoid expansion on UA dimensions in a systematic way, but rather on the feasibility and safety of this procedure and on the efficacy on respiratory events, daytime sleepiness and snoring.

Based on the presented results, hyoid expansion with the Air-Frame device is not suitable for the treatment of patients with obstructive sleep apnea. Only a small number of patients demonstrated clinically relevant improvement of the disease and there was a significant number of patients with a significant deterioration in the number of respiratory events. Regardless the low morbidity, the efficacy was limited.
The study protocol allowed 30 patients to enter the study. Since the efficacy results showed no significant improvement in AHI, it was decided to stop inclusion after 25 patients were included.

Feasibility of this procedure was good. In all cases we were able to split the hyoid bone and attach both parts of the Air-Frame system. It was important to identify the exact midline of the body of the hyoid bone to avoid a suboptimal position of the implant. Para- median position of the implant would result in unbalanced force on the 2 cornu of the hyoid bone. Because of the fixed positioning of the two parts of the implant on both sides of the midline-split hyoid bone, the amount of expansion was between 10-12 mm in all cases. No adjustability was possible after fixing the two parts together.

The tolerability of this procedure was good. Postoperative pain was mild to moderate and can be compared with a radiofrequency procedure of the palate (18).

The safety of the procedure was not compromised by technical issues during the procedure. The reported adverse events (AE) were procedure related in 1 case and device related in 1 case. The patient who developed pain in the neck after the procedure appeared to have a history of neck issues. Attention should be paid in those

patients with previous neck pain to position the head in limited extension during the procedure.
The patient who presented with granulation tissue at the site of the incision, was treated with local removal of the granulation. Anatomopathological analysis of this tissue showed many small bone particles all over the specimen without signs of foreign body reaction. It was concluded that the granulation tissue was probably caused by the numerous bone fragments caused by the sawing of the hyoid bone. After this AE occurred, rinsing was performed during the process of sawing to remove most bone particles before closing the wound.

The factors that determine the clinical efficacy of the Air-Frame system include patient selection, site of obstruction and the ability of the system to affect UA dimensions. Since this procedure targets the hypopharyngeal lateral walls, patients with clinical evidence of lateral wall collapse were included. Failure of clinical efficacy could partly be explained by the way true lateral wall collapse is clinically identified in this sample.
The effect of hyoid expansion on the UA dimensions was not evaluated in this study. It might well be possible that the procedure did not affect UA dimensions at all. This might be explained by a possible rotating movement where the 2 corns point inwards instead of an expanding movement outwards. The fact that we did not cut the insertion of the thyrohyoid membrane completely, might prevent the two parts of the dissected hyoid bone to expand sufficiently.

There are no other techniques for hyoid expansion. However, there are techniques that describe stabilization of the lateral walls. Maxillomandibular advancement is a highly effective procedure for OSA because it affects UA dimensions by moving the tongue base forward and by tensioning the lateral walls of the hypopharynx (19).

The strength of the statistical analysis is compromised by the small sample size, the study design (case series) and the fact that baseline polysomnography was not separated from screening.

Polysomnographic data, and AHI in particular, show important variability (20). The sample size of this study is small. Therefore only limited conclusions can be drawn from the objective outcome measures.
Both snoring and daytime sleepiness were significantly improved. Subjective improvement in the absence of objective improvement is described in various studies (21). This might be explained by variability of objective data, placebo-effect of the procedure and poor correlation between objective data and subjective outcome measures.

The data presented in this study do not support further use of this procedure or further trials with this device.

Conclusion

Hyoidexpansion with the Air Frame system does not decrease AHI. It results in significant reduction in daytime sleepiness and in snoring. In 5 patients the criteria for surgical success were reached. The rates of feasibility and safety were satisfactory. Further investigation of the impact of hyoidexpansion on UA dimensions is needed for better understanding the role of the lateral walls in obstructive sleep apnea. The presented technique was not able to stabilize the lateral wall of the upper airway.

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Chapter 5

A novel tongue implant for tongue advancement for obstructive sleep apnea: feasibility, safety and histology in a canine model

This chapter is based on the following publication:

Hamans E, Shih M, Roue C. A novel tongue implant for tongue advancement for obstructive sleep apnea: feasibility, safety and histology in a canine model. J Musculoskelet Neuronal Interact 2010;10:100-111.

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Introduction

Obstructive Sleep Apnea Syndrome (OSAS) is an underappreciated problem in our society resulting in social consequences and health concerns. A mounting body of evidence links the disorder to hypertension, stroke, cardiovascular morbidity and mortality (1), motor vehicle accidents (2) as well as a loss of productivity in the work-force. Treatments have been centered on behavioral modifications, medical treatments, dental and oral appliances, CPAP and surgical procedures to modify the predisposing anatomic abnormalities. There are multiple sites of obstruction identified (3) and successful treatment often requires a step-wise approach. The tonguebase is the target of some current treatments for OSAS (4). In some OSAS patients, the tongue base has been shown to collapse and contact the rear and side walls of the pharynx and/or the soft palate leading to airway obstruction. Various treatments including radiofrequency ablation and tongue advancement strategies (5) are used currently to increase the volume of the airway posterior to the tongue to prevent the tongue from obstructing the airway. OSAS has been studied in many different species of animals such as lambs (6), goats (7), pigs (8) and rabbits (9). A perfect model has not been found because naturally occurring sleep apnea has only been demonstrated in the English Bulldog (10). However, important information about the mechanism and potential adverse effects of the disorder has been learned through these animal studies.

The present study in canines reports on aspects of safety, feasibility and histology of a newly designed anchoring device implanted in the tongue and attached to the mandible. The device provides an advancement of the tonguebase, resulting in increased airway space and reduced tendency of the tongue to collapse during sleep, thereby reducing the occurrence of apneic events in the targeted population. No functional outcome measures were included in this study. The outcome of this study resulted in an investigational implant for adjustable tongue advancement in humans with obstructive sleep apnea (11).

Material and method

The present study was performed between August 2005 and February 2006 in a licenced animal laboratory (California, USA). All principles of laboratory animal care (National Institues of Health: publication No. 86-23, revised 1985) were followed.

Test article

The Advance System consists of three components: an anchor system (bone- and tissue anchor), the delivery system, and an implant removal system.

Anchor system: the anchor system comprises a tissue anchor (fig. 1) constructed from titanium alloy (Ti6Al4V) and Nitinol alloy (NiTi), a tether line constructed from Dyneema (DSM, The Netherlands), and a bone anchor (fig. 2) constructed from stainless steel alloy (316LV), and Nitinol alloy (NiTi). The bone anchor is attached to the mandible with titanium alloy (Ti6A14V) bone screws.

Figure 1. Tissue anchor

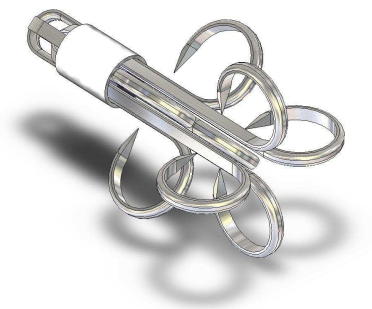
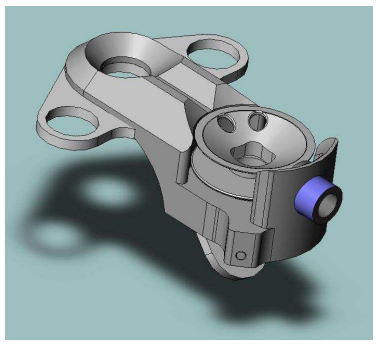


Figure 2. Bone anchor



Delivery system: the delivery system comprises an access trocar and cannula set used to tunnel into the genioglossal muscle to the intended location for the placement of the tissue anchor. A delivery handle is provided that will contain the tissue anchor in a delivery tube, advance the tissue anchor to the tip of the access cannula and deploy the tissue anchor into the tissue adjacent the tip of the access cannula. Also included in the delivery system is a snare for threading the tether line into the bone anchor, and an

adjustor tool to titrate the degree of tongue advancement. The delivery system is constructed from various stainless steel alloys and delrin polymer.

Implant removal system: the implant removal system consists of a tether line snare, and a tunneling trocar and cannula set. This system allows the user to remove the tissue anchor if desired. The tissue anchor may be removed either acutely at the time of the procedure, or after a period of healing has occurred.

The part numbers and lot numbers provide traceability to the test system. The Advance System components will be sterilized via autoclave. Sterilization process indicators are placed on the product packaging.

There is no control test article.

The following accessory devices may be used during this study: bone drill with 1.2 mm drill bit (MicroAire 6000 or similar), cross slot screw driver for 1.5 – 2.0 mm screws and standard surgical instrument set (scalpel, hemostats, scissors, retractors).

Test system

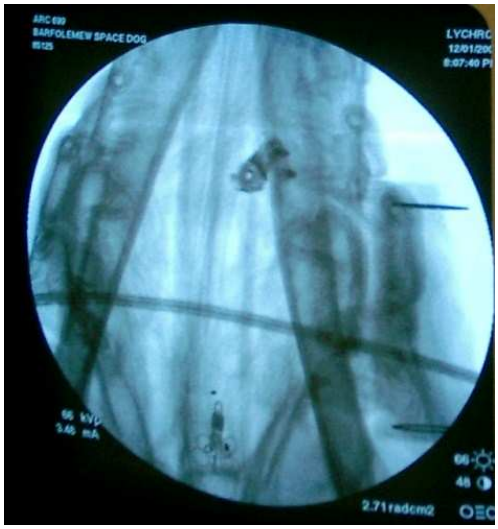
Twenty-one adult Hound crossbred canines a minimum of 6 months old are used in this study. The gender of the test system is not expected to influence the study results and either gender are used as provided by the animal source. At the onset of the study, the animals were experimentally naive. Adult animals selected for use in this study are as uniform in age and weight as possible. Their body weights range from 15 – 30 kg (ideally from 25 – 30 kg), and their exact age was commensurate with weight, but was a minimum of 6 months old. Animals were identified with a tattooed number.

Implantation

On the day of treatment the animals were anesthetized, weighed and instrumented to undergo the Advance procedure. Prior to the procedure, animals received 5mg/kg enrofloxacine IM once.

The implantation procedure involved the placement of a bone anchor in the mandible and a tissue anchor in the posterior tongue of canines. The treatment involved making an approximately 1-2 cm incision on the ventral aspect of the snout approximately 3 cm from the end of the snout. The Advance System was used to place the tissue anchor in the genioglossal muscle near the boundary between the genioglossal muscle and the intrinsic muscles of the tongue. An adjustable bone anchor was placed onto the mandible near the incision site, and the tether line attached to the bone anchor (fig. 3). Tension was placed on the tether line and tissue anchor by spooling the tether line onto the bone anchor using the adjustor tool. Following the titration of the tether line tension, the wound was closed in layers, the canine recovered and monitored. After the procedure, buprenorfine 0.01-0.05 mg/kg IM was administered once. Enrofloxacine 5mg/kg IM or PO SID was continued for a minimum of 7 days post procedure.

Figure 3. Fluoroscopy image of the implanted tissue anchor and bone anchor



Retrieval Procedure

At 1-2 weeks post-implantation, the animals were sedated, anesthetized, prepared, weighed and draped for aseptic procedures. Tools were not sterilized in those animals which were to be euthanized at the completion of the retrieval procedure. All animals were positioned for the study in a supine position. The anterior neck and chin was shaved and prepared. After the animal was prepared, the start time of the procedure was documented.

A small incision was made approximately coincident with the previous incision and proximate the estimated location of the bone anchor as determined by digital palpation. The titration needle was inserted through the incision and into the bone anchor. The spool was rotated clockwise and counterclockwise to verify the functionality of the adjustment mechanism and the security of the tissue anchor attachment to the bone anchor.

After verifying the functionality and security of the adjustment mechanism, blunt dissection was used to expose the bone anchor. The tether line was separated from the bone anchor by severing the knot on top of the bone anchor spool and pulling the tether line out of the bone anchor through the guide bushing. The tether lines were threaded into the retrieval system and gripped with the winding tool or a needle driver per the evaluator's preference. Blunt dissection was used to expose additional tether line as necessary to allow the user to get an adequate hold on the tether line by wrapping it several times around the winding tool or needle driver. The retrieval tool was then advanced along the tether line until the proximal hub of the tissue anchor was reached with the dilator tip,verified with fluoroscopy and palpation. The cannula was then further advanced over the tissue anchor while maintaining tension on the tether line until the tissue anchor was fully retracted into the retrieval tool.

Twenty-one canines were used in this study. The study population was divided in 4 subgroups. Implantation of the Advance System was performed in different groups for different purposes. The subgroups are presented in table 1.

Table 1. Devices Design Subgroups

Subgroup	Description	Comments
A	Early Development Group	2 samples at 122 and 150 days post-implant. Early anchor designs & delivery/retrieval tools
B	Development Group	3 samples at 84 days. Close to final design & procedure
C	Pre-clinical Group – single fixation screw	2 samples at 30 days of the final implant design placed with one fixation screw and 3 samples at 30 days with 1 extra screw placed at revision procedure
D	Pre-clinical Group – multiple fixation screw	11 samples at 30 to 180 days post-implant representing the final design, materials and implantation procedure.

Outcome measures

Evaluation of the implant and the implanted animals were conducted at the time of implantation, at 30 days, 60 days, 90 days, 120 days and 150 days. At each evaluation some animals were sacrificed for histological analysis of the implant and surrounding tissues.

Implant procedure: feasibility was evaluated by measuring the procedure time, length of incision, implantation depth and location, amount of advancement and presence of technical or clinical adverse events.

Retrieval procedure: feasibility of attaching the tether winder to suture, feasibility and safety of accessing the tissue anchor with dilator, recapturing the tissue anchor into the recapture tube and controlling the integrity of the recaptured tissue anchor.

Each animal was clinically evaluated for the presence of infection, seroma formation, hematoma, implant extrusion or exposure, vocalisation and eating pattern at each of the follow-up examinations.

Samples of mandibular bone (bone anchor) and lingual soft tissue (tissue anchor) were harvested from 21 dogs with four distinctive subgroups at specified time points (table 1). At each time point, the assigned animals were sacrificed and the bone, soft tissues, and associated anchors were removed. The bone anchors and fixation screws were evaluated for stability on the mandible. Finally the specimens were fixed in 10% formaldehyde for histological preparation and evaluation.

The specimens were exposed to soft x-ray to obtain contact radiographs for proper identification of the location and orientation of the anchors in mandible and in lingual tissues. The specimens were trimmed using an EXAKT™ saw to obtain the desired tissue slices, approximately 5 mm thick. The mandibular bone with the bone anchor was prepared in a coronal plane of the jaw through the middle of the anchor (approximately 1 cm x 1 cm x 1.2 cm). A mid sagittal plane was used to prepare the lingual anchor (approximately 1 cm x 1.5 cm), possibly including some portion of the tether line.

The slices were dehydrated and cleared using an automatic processor. Slices were infiltrated and embedded in methylmethacrylate (MMA) medium and sectioned to obtain one 200 ± 50um thick slide using the EXAKT™ saw. The slides were ground to about 50 um thick and then stained with toluidine blue.

Histopathological assessment of the stained slides was performed to determine the general tissue responses and bone integration. Scoring criteria for the histopathology is summarized in Table 2. Severity of infiltration of lymphocytes and presence of polymorphonuclear cells are evaluated as a measure of local inflammation. Presence of macrophages and giant cells is evaluated as a measure of the activation of local defence against foreign bodies. Histological analysis was performed on all specimens.

Table 2. Histopathological Scoring Criteria

	Characteristic	***Grading***	***Score***
I.	Severity on infiltration of lymphocytes	Severe	4
		Moderate to severe	3
		Moderate	2
		Mild	1
		None	0
	Presence of polymorphonuclear cells	Marked	4
		Moderate to marked	3
		Moderate	2
		Mild	1
		None	0
	Presence of macrophages	Marked	4
		Moderate to marked	3
		Moderate	2
		Mild	1
		None	0
	Presence of giant cells	Marked	4
		Moderate to marked	3
		Moderate	2
		Mild	1
		None	0
	Extent of fibrous encapsulation	Severe	4
		Moderate to marked	3
		Moderate	2
		Mild	1
		None	0
	Maximum score of section I		**20**
II.	Bone growth at implant site	Marked	4
		Moderate to marked	3
		Moderate	2
		Little	1
		None	0
	Sub total of section II		**4**
III.	Bone lysis around implant site	Marked	4
		Moderate to marked	3
		Moderate	2
		Little	1
		None	0
	Sub total of section III		**4**

Results

Implant procedure

All 21 implant procedures were successfully completed without complications. No device failures or malfunctions were observed at the time of implantation. The average procedure time was 53.5 minutes (range: 36-81 minutes). The average incision length was 27.5 mm (range: 20-43 mm). The tissue anchor was advanced an average of 13.5 mm (Range: 6.7–22.3 mm). The average depth of implantation (canula insertion) was 6.6 cm (range 5.5 – 7.5 cm).

During the procedure, no complications were observed such as: perforation of the oral cavity, difficulty inserting trocar or delivery system into tongue, vessel perforation, excessive bleeding, damage to the mandible, fracture or failure of any part of the implant or delivery system, excessive force required or other difficulty with titration. The implanting investigator was able to palpate the delivery system and successfully deliver the tissue anchor in the desired location.

Retrieval procedure

The feasibility of attaching the tether winder to the suture, the feasibility and safety of accessing the tissue anchor with the dilator and the recapturing of the tissue anchor into the recapture tube was rated clinically acceptable in all cases. All tissue anchors were intact after retrieval.

Follow up evaluation

During the early follow-up periods (up to 30 days), five of the canines showed wound infection and four showed a seroma at the surgical incision site. All the infections and seromas resolved with antibiotic treatment without the need for surgical intervention. None of the canines demonstrated any other significant health issues during the in-life phase of the study. All canines vocalized normally, ate normally, and showed no signs of distress or pain that might be indicative of damage to or impingement on nerves. No

device extrusions into the oral cavity or through the skin have been noted at any time point in any of the implanted animals. On gross examination, the tongue, oral cavity and mandible implantation areas appeared normal during the in-life follow-up examinations and at the time of their removal for histology.

Of the 14 bone anchors secured with two fixation screws in this study, only one bone anchor showed signs of instability. In this animal, the central screw affixing the bone anchor was not adequately seated and tightened at the time of implantation. Four out of seven bone anchors secured with a single fixation screw loosened during the study period.

Histology

Group A: early development:

The samples of 2 canines were harvested at 122 days (533335) and 150 days (527939). The tissue reaction to the bone anchor was similar and mild in both animals, while the lingual anchors had large variations in the amount of lymphocyte and the presence of giant cells.

Results of histologic evaluation is presented in table 3.

Table 3. Histopathology Scores on Bone and Tissue Anchors – Group A

Bone Anchor							
Animal ID	**Lymphocytes**	**PMN**	**Macrophages**	**Giant cells**	**Fibrosis**	**Bone Growth**	**Bone Lysis**
533335	1	1	1	1	2	1	0
527939	1	1	1	1	1	1	0
Tissue Anchor							
Animal ID	**Lymphocytes**	**PMN**	**Macrophages**	**Giant cells**	**Fibrosis**		
533335	1	0	2	2	1		
527939	4	0	2	0	1		

Figures 4 and 5 show histologic images of the bone anchor and tissue anchor at 150 days after implantation.

Figure 4. Bone anchor 150 days: left: early development bone anchor (527939), 10X magnification, right 100X magnification. Toluidine blue stained. Bone remodeling was observed by the presence of bone resorption and bony proliferation adjacent to the screw and the mandible and on the periost.

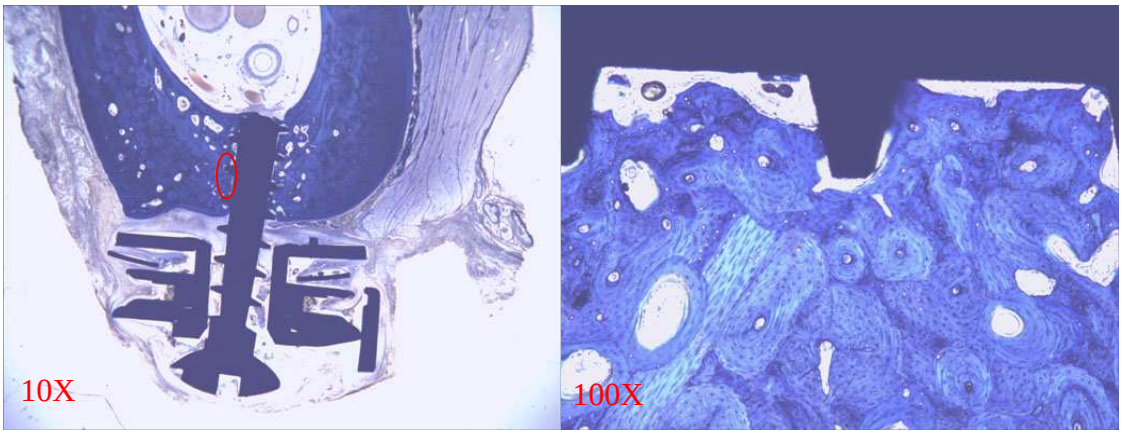
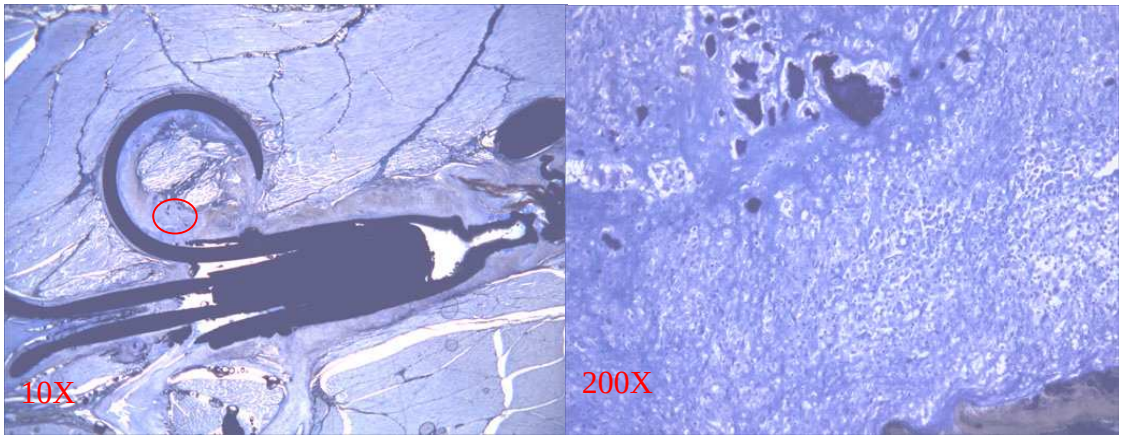


Figure 5. Tissue anchor at 150 days: left: early development lingual anchor (527939), 10X magnification, right: 200X magnification. Toluidine blue stained. The tissue anchor is incorporated in the tongue muscle with a thin fibrous covering without inflammation outside this fibrous layer.



Group B: development:

The samples of three canines were harvested at 84 days. The tissue reactions to the bone anchor and lingual anchor had large variations in all parameters. Animal 518611 contributed the most to the variations, while the other two had mostly mild tissue

reactions. Bone growth and lysis in that case might have resulted from the tissue reactions. Results of histologic evaluation is presented in table 4.

Table 4. Histopathology Scores on Bone and Tissue Anchors – Group B

Bone Anchor							
Animal ID	**Lymphocytes**	**PMN**	**Macrophages**	**Giant cells**	**Fibrosis**	**Bone Growth**	**Bone Lysis**
518174	1	1	1	1	1	1	1
518611	3	3	2	2	3	3	2
518786	1	1	1	0	2	1	1
Tissue Anchor							
Animal ID	**Lymphocytes**	**PMN**	**Macrophages**	**Giant cells**	**Fibrosis**		
518174	2	1	2	1	1		
518611	4	2	4	1	2		
518786	1	0	2	2	1		

Figures 6 and 7 show histologic images of the bone anchor and tissue anchor at 84 days after implantation.

Figure 6. Left: pre-study development bone anchor at 84 days (518174), 10X magnification, right: 200X magnification. Toluidine blue stained. A dense fibrous layer is observed between the bone anchor and the mandible.

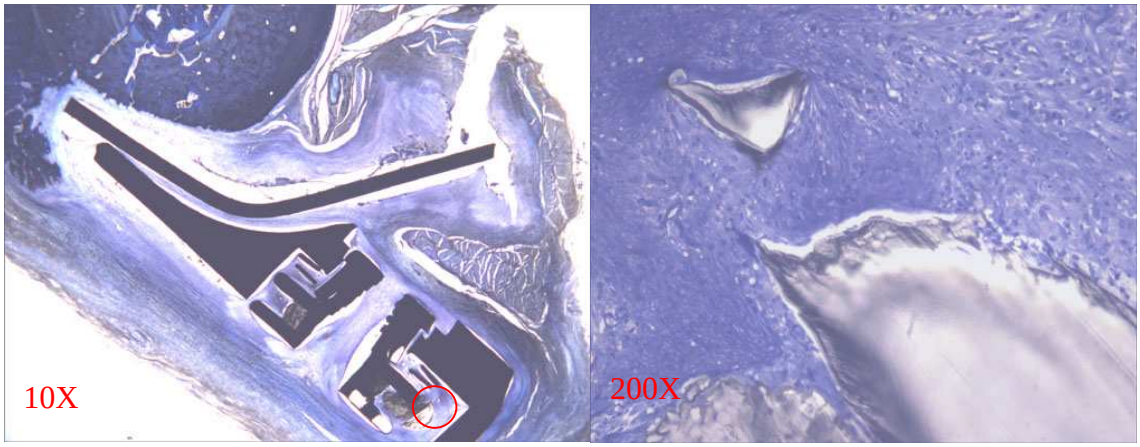
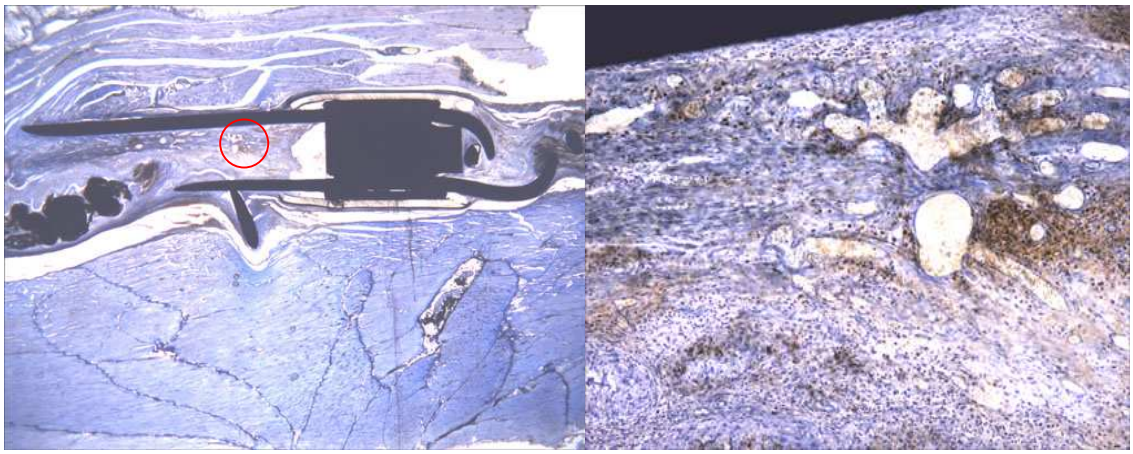


Figure 7. Left: pre-study development lingual anchor at 84 days (518174), 10X magnification. Right: 100X magnification. Toluidine blue stained. A fibrous layer of 1 mm encapsulates the tissue anchor (left). No inflammation is seen outside this fibrous layer. Moderate inflammation is observed within the interior portions of the fibrous layer (right).



Group C – Pre-Clinical Single Fixation Screw

Two of the five samples (529427 and 541672) had a single fixation screw and were harvested at 30 days. The other three samples (537900, 543608 and 543888) were harvested at 30 days and were originally implanted with a single fixation screw and had a second screw added in a revision surgery. The tissue reactions to the bone anchor and lingual anchor had large variations in all parameters among these five samples. Results of histologic evaluation is presented in table 5. Figures 8 and 9 show histologic images of the bone anchor and tissue anchor at 30 days after implantation.

Figure 8. Left: pre-clinical single fixation screw bone anchor at 30 days (529427), 10X magnification. Right: 100X magnification. Toluidine blue stained. The original cortical bone is located at top. A band of lighter blue stained bony tissue separates the newly formed woven bone that is perpendicular to the band. Strings of Sharpey's fibers can be seen from the surface of newly formed bone.

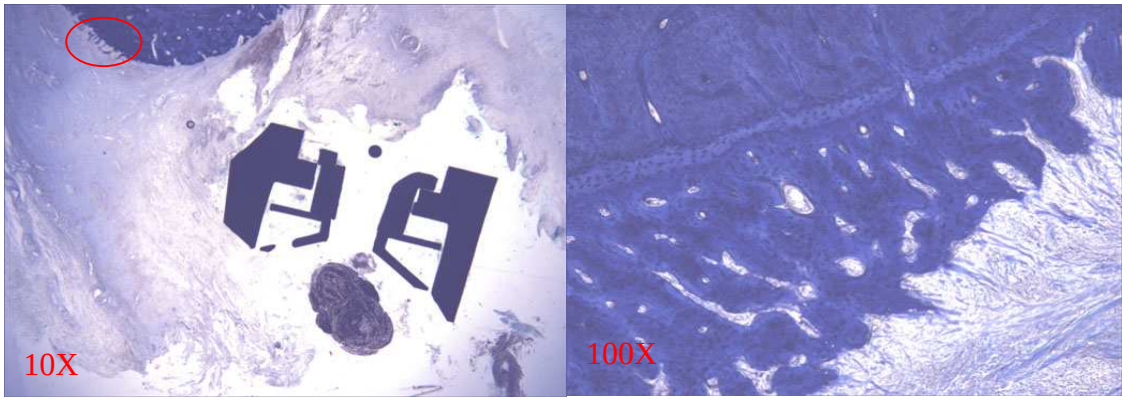


Figure 9. Left: pre-clinical single fixation screw lingual anchor at 30 days (541672), 10X magnification. Right: 100X magnification. Toluidine blue stained. The implant part is seen at the top left corner. The tissues seen around the implant part contain many newly formed vessels and obvious infiltration of inflammatory cells.

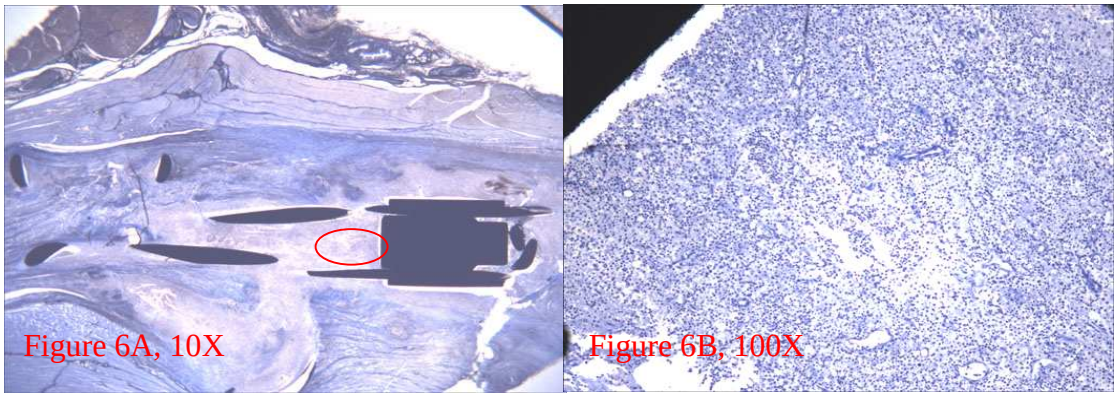


Table 5. Histopathology Scores on Bone and Tissue Anchors – Group C

Bone Anchor							
Animal ID	**Lymphocytes**	**PMN**	**Macrophages**	**Giant cells**	**Fibrosis**	**Bone Growth**	**Bone Lysis**
529427	1	1	1	0	2	2	0
541672	2	2	1	0	2	2	2
537900	1	2	2	1	1	2	1
543608	2	2	3	1	2	1	2
543888	1	2	1	1	1	1	1
Tissue Anchor							
Animal ID	**Lymphocytes**	**PMN**	**Macrophages**	**Giant cells**	**Fibrosis**		
529427	4	4	2	1	2		
541672	4	2	4	2	2		
537900	3	3	3	1	2		
543608	1	1	1	2	1		
543888	4	1	3	1	1		

Group D – Pre-Clinical Multiple Fixation Screws

Eleven animals were implanted with the Advance device utilizing two fixation screws. Of these animals, two were sacrificed at 30 days, five at 90 days, and four at 180 days post-implantation. Results of histologic evaluation of the bone anchor is presented in table 6.

Table 6. Histopathology Evaluation on Bone Anchors – Group D

Bone anchors Pre-Clinical Evaluation Group								
Animal ID	**Time Points**	**Lymphocytes**	**PMN**	**Macrophages**	**Giant cells**	**Fibrosis**	**Bone Lysis**	**Bone Growth**
544990	30	1	0	1	1	3	1	3
MOVF34152	30	2	2	1	0	2	0	2
30 day average		**1.5**	**1.0**	**1.0**	**0.5**	**2.5**	**0.5**	**2.5**
2X128	90	1	0	1	1	3	0	1
35153	90	2	3	2	1	1	3	3
85125	90	1	2	2	1	1	0	4
34189	90	1	0	2	2	3	1	1
54253	90	2	3	2	1	1	1	3
90 day average		**1.4**	**1.6**	**1.8**	**1.2**	**1.8**	**1.0**	**2.4**
24253	180	1	3	2	1	2	1	2
545031	180	1	0	1	1	3	0	2
34325	180	1	0	1	1	3	0	2
24382	180	1	0	1	1	1	0	1
180 average		**1.0**	**0.8**	**1.3**	**1.0**	**2.3**	**0.3**	**1.8**

Figures 10 and 11 show histologic images of the bone anchor at 90 and 180 days after implantation.

Fig. 10. Bone anchor at 90 days. Left: screw with fibrous tissue and some bone attachment. Right: direct bone apposition to implant.

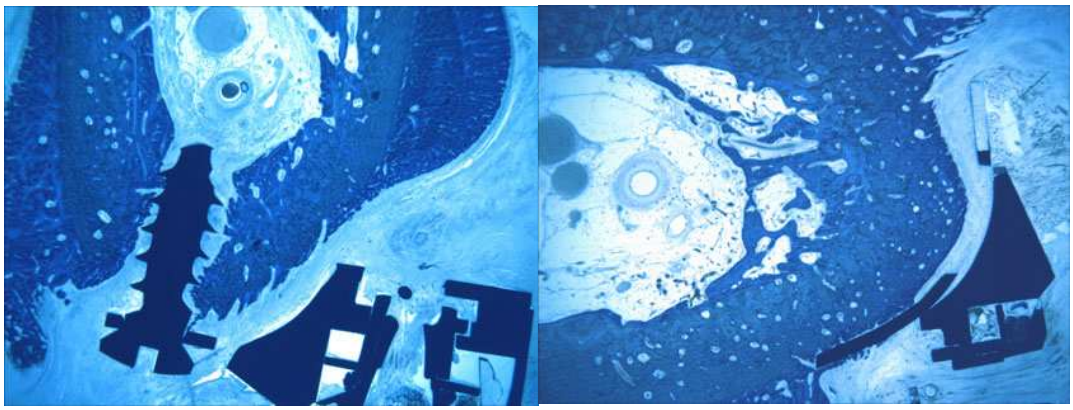
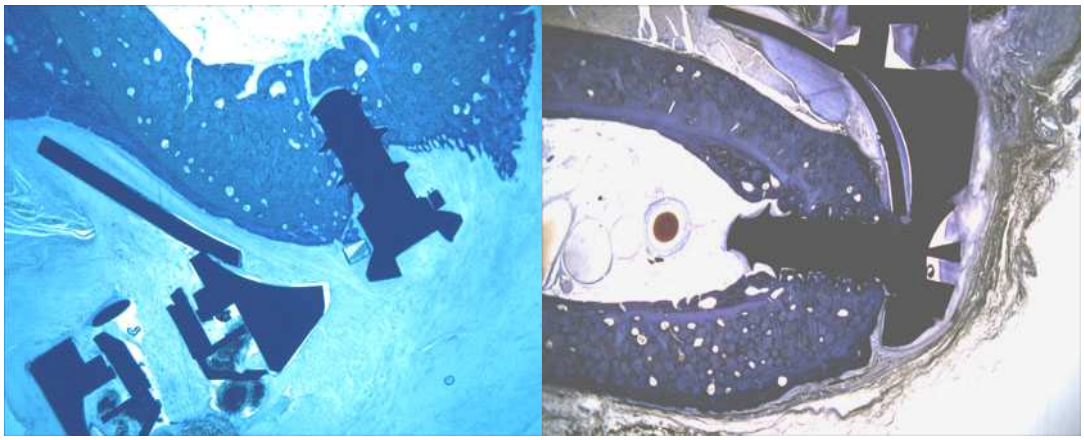


Fig. 11. Bone anchor at 180 days. Seamless screw-bone apposition is seen in both slides and bone proliferation in response to mechanical stresses.



Bone anchor histology:

A dense fibrous layer was seen between the bone anchors and the mandible (fig. 6) with direct bone apposition to the screws and/or implant seen in most of the slides at the 90 (fig. 10) and 180 (fig.11) day timepoints. A 2 to 8 mm thick tissue reaction zone was seen around the bone anchors at 30 days. Outside this reaction zone, normal tissues were present without signs of inflammation. In addition, the width of the zone reduced to a thin layer at 180 days from about 2 mm to 8 mm at 30 days. Bone remodeling was demonstrated at 150 days by bone resorption adjacent the interface of the bone anchor and mandible and bony proliferation on the lateral periosteal and ventral endosteal surfaces (fig. 4 and fig. 8).

Results of histologic evaluation of the tissue anchor is presented in table 7. Figures 12 and 13 show histologic images of the tiisue anchor at 30 and 90 days after implantation.

Table 7. Histopathology Evaluation on Tissue anchors – Group D

Tissue anchors Pre-Clinical Evaluation Group						
Animal ID	**Time Points**	**Lymphocytes**	**PMN**	**Macrophages**	**Giant Cells**	**Fibrosis**
544990	30	1	0	2	1	1
MOVF34152	30	4	1	4	1	2
30 day average		**2.5**	**0.5**	**3.0**	**1.0**	**1.5**
2X128	90	1	1	2	2	2
35153	90	3	2	3	1	1
85125	90	3	1	3	2	2
34189	90	1	0	2	1	1
54253	90	3	2	3	1	1
90 day average		**2.2**	**1.2**	**2.6**	**1.4**	**1.4**
24253	180	1	1	1	1	1
545031	180	1	0	1	1	1
34325	180	1	0	1	1	1
24382	180	1	0	1	1	1
180 day average		**1.0**	**0.3**	**1.0**	**1.0**	**1.0**

Fig. 12. Tissue anchor at 30 day. Tissue anchor is incapsulated in thin layer of fibrous tissue surrounded by normal muscular tissue.

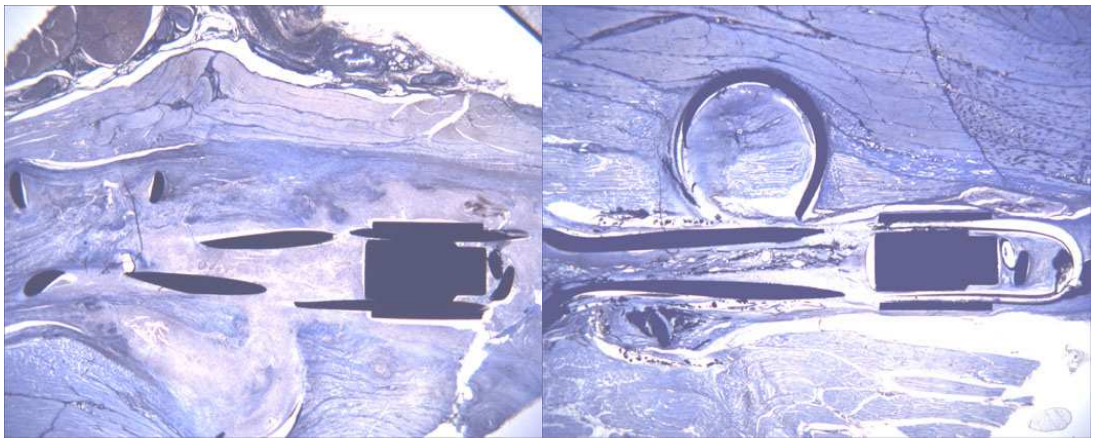
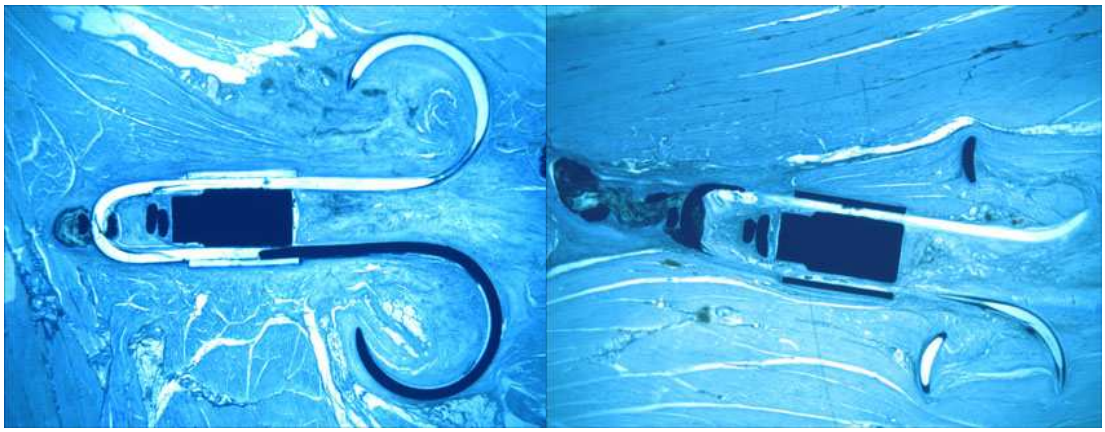


Fig. 13. Tissue anchor at 90 days. Tissue anchor is incapsulated in thicker layer of fibrous tissue surrounded by normal muscular tissue.



Tissue anchor histology:

Grossly, the tongue and mandible appeared normal in all the samples submitted for analysis. After dissection and slide preparation, histopathological analysis of the tissue anchor showed similar tissue components at all three time points, and the severity of the tissue reactions reduced with time. A thin 0.5 to 1.0 mm thick fibrous layer encapsulated the tissue anchor at each time point (fig. 5 and fig. 12). Histologically normal striated muscle was seen surrounding the encapsulated tissue anchor. The tissue anchor is incorporated into the tongue muscle with a thin fibrous covering without inflammation of the tongue muscle outside the fibrous layer and mild to moderate inflammation observed within the interior portions of the fibrous layer (fig. 7 and fig. 9). The points of the tissue anchor barbs did not appear to cause any clinically significant effects such as erosion or chronic irritation of the muscle tissue. The lack of residual fibrous tissue dorsal to the tissue anchor indicates the tissue anchor was stable in the tongue muscle with no evidence of migration through the tongue or other instability. The tissue anchor was well-tolerated within the tongue muscle and was well-healed in all the samples at 180 days.

Discussion

This study is an evaluation of the feasibility and safety of a new tongue implant for the treatment of obstructive sleep apnea. Histologic analysis of the two parts of the implant was performed to evaluate tissue reaction and stability of the implant in canines.
The fact that all procedures were performed successfully and no device failures or complications were reported resulted in a novel procedure under investigation for treatment of obstructive sleep apnea that is safe and feasible in humans.

Some canines showed wound infection or seroma. These infections were related to difficulty in wound management and cleanliness of the surgical site in the canine model. The seromas appeared to be related to the inability to place a suitable drain in the snout of the canine due to the attending increase in infection risk associated with the placement of drains in canines.

One bone anchor secured with 2 fixation screws showed signs of instability. Four bone anchors secured with one single screw loosened during the study period. In the final design of the bone anchor for human implantation, the bone anchor will be secured with three screws which will further enhance the stability.

Histologic evaluation of the bone anchor and tissue anchor showed only limited inflammation at 30 days. This inflammation decreased over time.
The tissue anchor was incapsulated in a fibrous layer. This finding is in accordance with other studies evaluating titanium biocompatibility (12). The surrounding muscle tissue was free of inflammation. These findings support the biocompatibility of the implant. The implant is well tolerated by the canine tongue.

Around the bone anchor, bone reformation and remodelling could be in favor of the stability of the implant fixed in the mandible. This remodeling is apparently in

response to the biomechanical loading of the bone anchor and mandible due to the tension supplied by the tissue anchor connection. The strings of Sharpey fibers are probably the result of the traction of the bone anchor on the mandible. Bone matrix was particularly abundant and thick at 150 days, indicating progressive mineralization and maturation of remodeled bone matrix and compatibility of the implant (13).

Local inflammation around the bone anchor and tissue anchor are mild and decrease over time (table 4). Foreign body reaction around both parts of the implant are mild in the early phase after implantation, have the tendency to increase at 90 days and decrease again at 180 days. The presence of giant cells was observed by other investigators using titanium bone screws in the mandible (14).

Conclusion

The implantation of the Advance™ System is safe in the canine model. Technical success was achieved in all dogs clinically. There were no procedural complications observed that required revision. The seromas and infections noted during the in vivo portion of the study did not appear to adversely affect the healing of the implanted components nor involve or originate from the implants.

The implant devices are well-tolerated in the canine as evidenced by gross examinations in-life and post-mortem as well as histopathological examination of the explanted tissues and devices. No adverse health consequences or other complications on the mandible or tongue of the canines related to the implant were evident with up to 16.5 mm of advancement. Infections and seromas observed within the study are related to wound management difficulties specific to the canine model which are not relevant to human clinical cases. Histological evaluation indicates good healing responses for both the tissue and bone anchors. The bone anchor appeared to be stable in position to the mandible in all cases where the bone screws were sufficiently secured in the intended places, and the mandible exhibited a remodeling response

accommodative to the biomechanical loading of the bone anchor. Histology of the tissue anchors showed a thin fibrous layer encapsulating the tissue anchor, and a lack of tissue anchor migration at time points up to 180 days as evidenced by a lack of a residual trail of fibrous tissue distal to the anchor. The components of the Advance™ system were found to be benign, well-tolerated, and suitable for implantation in the tongue.

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Chapter 6

Adjustable tongue advancement for obstructive sleep apnea: a pilot study.

Presented at:

World Congress of Sleep Apnea, 26 March 2009 in Seoul.

This chapter is based on the following publication:

Hamans E, Boudewyns A, Stuck B, Baisch A, Willemen M, Verbraecken J, Van de Heyning P. Adjustable tongue advancement for obstructive sleep apnea: a pilot study. Ann Otol Rhinol Laryngol 2008;117:815-823.

Antwerp University Hospital (Belgium), University Hospital Mannheim (Germany).

Abstract

Objective:

Surgical treatment of obstructive sleep apnea caused by hypopharyngeal collapse of the upper airway can be considered in patients who are intolerant to CPAP. Present procedures addressing the hypopharynx are invasive, have a substantial morbidity and limited efficacy.

Methods:

Ten patients (mean age 44 y) with moderate to severe OSAS (15<AHI<50) with CPAP intolerance were included in a prospective, non-randomized, multicenter study to evaluate the feasibility, safety and efficacy of a novel tongue advancement procedure. The procedure consist of the implantation of a tissue anchor in the tonguebase and an adjustment spool at the mandible. Titration of this tissue anchor results in advancement of the tongue and a patent upper airway.

Results:

AHI decreased from 22.8 at baseline to 12.9 at six month follow-up (p=0.009). Epworth Sleepiness Scale decreased from 11.6 at baseline to 7.4 at six month follow-up (p=0.094) and snoring decreased from 7.7 at baseline to 3.8 at six months follow-up (p=0.005). Four technical adverse events were noted and one clinical adverse event occurred.

Conclusion:

Adjustable tongue advancement is a feasible and relatively safe way to reduce AHI and snoring in selected patients with moderate to severe OSAS and CPAP intolerance. Technical improvements and refinements to the procedure are ongoing.

Keywords: obstructive sleep apnea, hypopharynx, tongue base, sleepsurgery

Introduction

Obstructive sleep apnea syndrome (OSAS) is a sleep related breathing disorder caused by repeated partial or complete collapse of the upper airway which can be diagnosed in 4% of middle aged men and 2% of women (1). These moments of collapse, called “respiratory events”, cause apnea, hypopnea, increased upper airway resistance and oxygen desaturation, or a combination of these. As a consequence of these events, frequent arousals occur during sleep resulting in daytime symptoms like hypersomnolence (2) and fatigue, concentration-impairment and increased incidence of traffic accidents (3). Standard treatment for moderate to severe OSAS is nasal continuous positive airway pressure (CPAP) (4).

Planning for surgical treatment of OSAS starts with evaluation to determine the most likely site(s) of upper airway (UA) narrowing or collapse. The soft palate and tongue base are the most common sites of UA obstruction in OSAS.

Palatal surgery was introduced by Fujita in 1981 (5,6). The response rate of uvulopalatopharyngoplasty (UPPP) in unselected patients with OSA was 41% (7). These poor results are probably caused by tonguebase involvement during collapse, where a palatal procedure alone will not result in optimal improvement. New hypopharyngeal procedures are to be investigated in order to improve those patients with hypopharyngeal collapse (type III according to Fujita) (5) or with multilevel collapse (type II).

Several hypopharyngeal procedures have been developed in order to achieve higher response rates in patients with hypopharyngeal obstruction. Most of the studies that report on results of these procedures are supported by level 4 evidence (8,9). Intolerance and/or poor adherence to CPAP, limited clinical effect of the present hypopharyngeal procedures and lack of minimal morbidity procedures justify innovative research for new procedures that address the hypopharyngeal region of the upper airway.

The present study investigates the feasibility, safe and efficacy of a novel procedure for adjustable tongue advancement to stabilize the tongue in OSAS patients with type III (mainly tonguebase) obstruction. The Advance™ System, which is implanted in a reversible procedure, consists of a lingual tissue anchor and mandibular titration spool that provides for adjustable advancement and stabilization of the tongue base.
The purpose of this paper is to introduce the Advance™ System as a novel procedure that addresses the hypopharynx, to emphasize the technology and method of implantation and to present the preliminary results concerning feasibility, safety and efficacy.

Materials and methods

In a prospective, phase 1, non-randomized study, the feasibility, safety and efficacy of the Advance™ System were evaluated. The study protocol allows 30 patients to enter the study with a follow-up time of 1 year. This report evaluates the preliminary results of the first 10 patients at 6 month follow-up.

Study Design

This prospective, multicenter, single arm pilot study started in February 2006 at the University Hospital Antwerp in Belgium and in May 2006 by the University Hospital Mannheim in Germany. From the 10 patients in this evaluation, 9 were treated in Antwerp and 1 in Mannheim. The study was approved by the Ethics Committee of both institutions.

Inclusion into the study (table 1) required a history of moderate to severe OSAS (screening apnea-hypopnea-index (AHI) between 15 and 50), body mass index (BMI) of 32 or less, refusal or non-compliance to continuous positive airway pressure (CPAP) therapy, age of between 18 and 65 and evidence of tonguebase obstruction. Selection for tonguebase obstruction was performed by clinical and endoscopical (Müller manoeuvre) examination of the awake patient and/or by sleep endoscopy (10).

TABLE 1. STUDY CRITERIA

Inclusion Criteria
Diagnosed with obstructive sleep apnea (15 ≤ AHI ≤ 50)
Age ≥ 20 and ≤ 65 years old
Body mass index ≤ 32 (kg/m^2)
Refused or failed CPAP treatment
Identified evidence of airway collapse at base of tongue
Exclusion Criteria
Prior obstructive sleep apnea surgery
Enlarged tonsils (3+ & 4+)
Unsuitable anatomy for implant
Severe retrognathia
Rhinitis or nasal obstruction
Unable to comply with follow up visits
Women who are pregnant or breastfeeding
Active systemic infection
Allergy to medication used during implant
History of neck/upper respiratory tract cancer
History of radiation therapy for neck/upper respiratory tract
Dysphagia
Major cardiovascular and/or pulmonary disorders
Other medical/social/psychological disorder that preclude them from study
Enrollment in another study

CPAP = continous positive airway pressure

Patients with clear hypopharyngeal obstruction during Müller manoeuvre and/or during sleep endoscopy were eligible for the study. Patients with prior airway surgery (except tonsillectomy, adenoidectomy or nasal surgery), enlarged tonsils (3+ or 4+), severe retrognathia or dysphagia were excluded from enrollment. Patient characteristics are shown in table 2.

TABLE 2. PATIENT CHARACTERISTICS

n=10	Average	Range	Standard deviation
Age (yr)	44	(27 – 60)	10.0
Sex	M (100%)	–	–
BMI (kg/m^2)	26.6	(23.0 – 31.6)	2.7

Since the inclusion criteria were stringent, inclusion of patients took more time than expected. This study only included a highly selected group of CPAP intolerant patients having clinical signs of type III obstruction.

Implant

The Advance™ System consists of a tissue anchor with eight self engaging struts and pre-attached tether line, a titration spool with three holes to accommodate fixation to the inferior rim of the mandible, a trocar and cannula to facilitate access into the tongue base, a delivery system which allows for implantation of the tissue anchor through the trocar and a titration needle which allows for adjustment of the forward tension of the tissue anchor either during or after the implantation procedure. In addition, to facilitate removal of the system if necessary, a recapture system has been developed.

Implantation Procedure

The patient is positioned in the supine position with the head extended. The submental region is prepared sterile, while the oral region is prepared separate in order to have access to the mouth while keeping the submental region sterile. Under general anesthesia with nasal intubation and antibiotic prevention (2 gram cefazolin), a 2 cm submental horizontal incision is made. Using blunt dissection, cautery and a periosteal elevator, a 1 cm x 5 mm portion of the inferior mandible at midline is prepared to accommodate the adjustable titration spool. Once a proper location is prepared, the trocar and cannula kit is used to gain access to the tongue base. Using digital palpation of the tongue with one non-sterile hand and, if necessary, with the use of fluoroscopy, the trocar is inserted into the genioglossus muscle and advanced posteriorly toward the base of tongue near the circumvallate papillae and approximately 1 cm from the dorsum (Figure 1). The trocar is then removed from the cannula and replaced by the delivery system (Figure 2). The tissue anchor is deployed from the delivery system and prior to removing the delivery system, traction is placed on the tissue anchor to insure adequate advancement of the tongue is possible in its

present location. If necessary, the tissue anchor can be withdrawn back into the delivery system in order to reposition it to an optimal location. The tether line is threaded to the titration spool, which is then mounted to the mandible with three fixation screws. The tether line is tied to the titration spool with a figure 8 knot and the titration needle is used to rotate the spool until the excess line is taken up. The wound is closed in two layers and a suction drain is left in place.

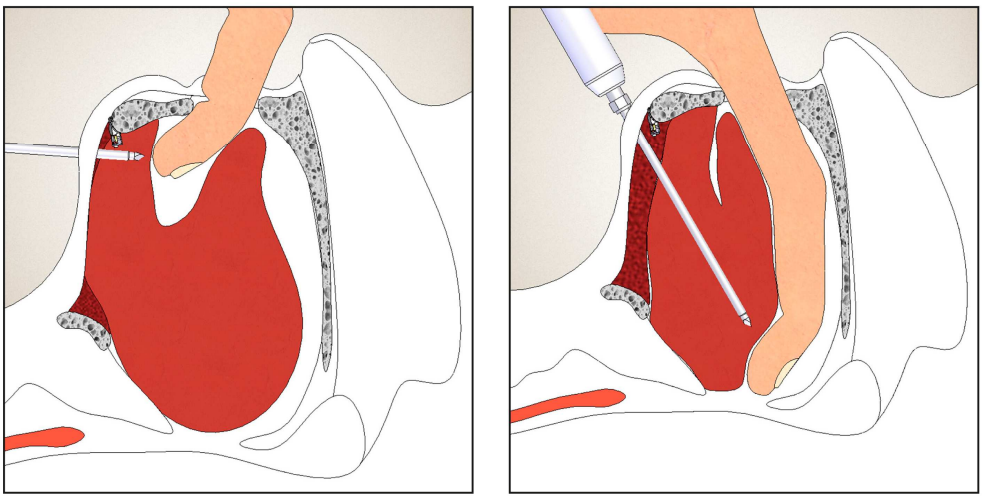


FIGURE 1. Introduction of trocar. Left: Introduction of trocar/cannula into the genioglossus using digital palpation. Right: Positioning trocar at base of tongue approximately at the circumvallate papillae.

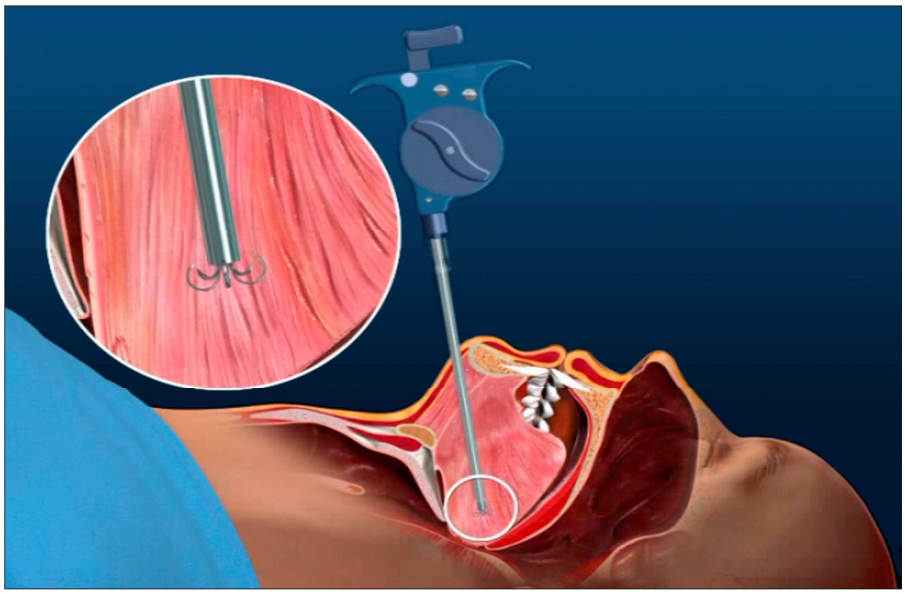


FIGURE 2. Delivery of the tissue anchor into the tongue with the delivery system

Titration

Two to four weeks after implantation, patients underwent a titration procedure in an outpatient setting, which resulted in advancement of the tongue.

During the titration procedure, the patient is placed in supine position. A local anaesthetic (lidocaïne 1%) is administered at the site of the titration spool. The patient is sedated (propofol titration and midazolam) to achieve a state of drug-induced sleep where the patient is breathing spontaneously but shows clear signs of obstructed breathing and snoring. A small, 2 mm submental incision is made and the titration spool is engaged with the titration needle (Figure 3). Fluoroscopy was available in order to facilitate the engagement. By rotating the spool with the titration needle, the tissue anchor is advanced until an improvement in the airway patency is observed with either flexible endoscopy, a decrease in snoring, a decrease in obstructive breathing or via fluoroscopy (figure 4).

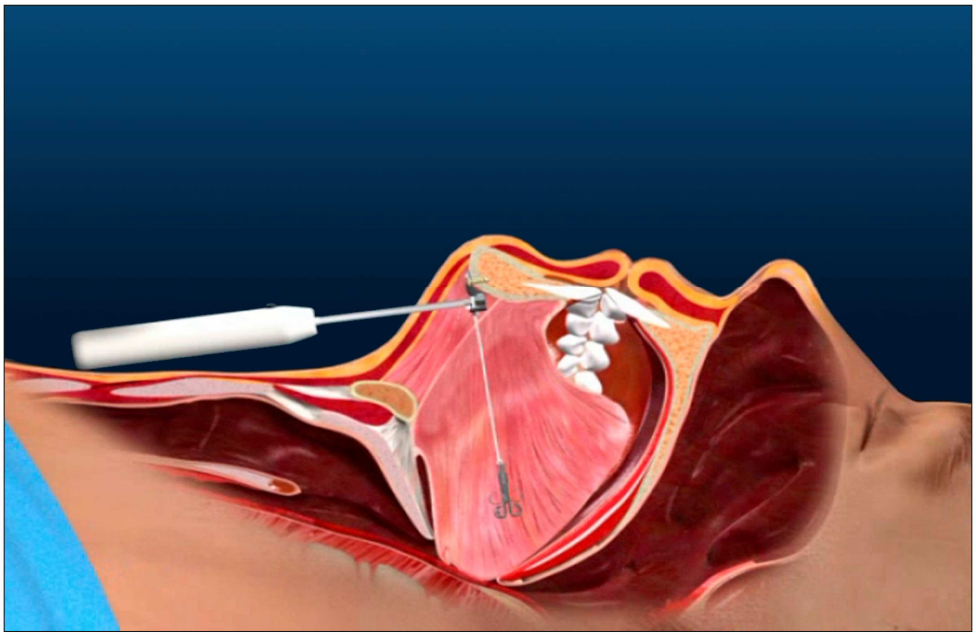


FIGURE 3. Titration Procedure: Patient in supine position, under local anesthesia with sedation, the tissue anchor is advanced with the titration needle until an improvement in airway patency is observed.

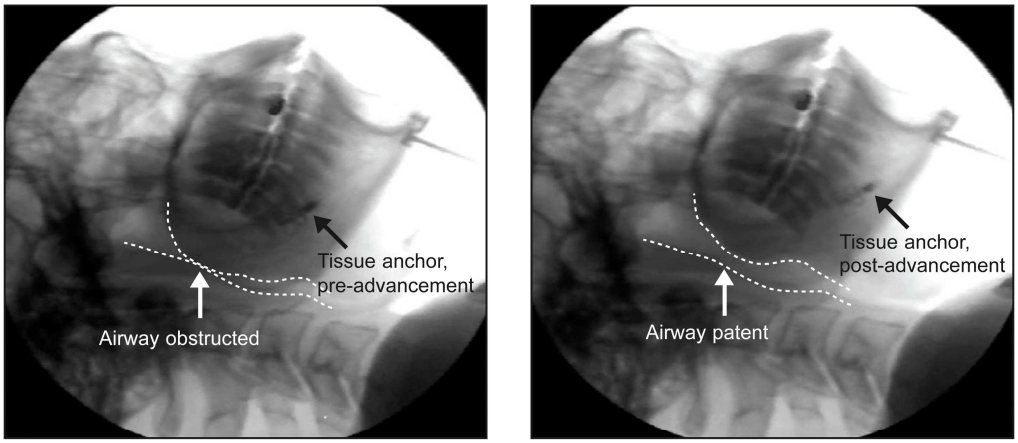


FIGURE 4. Fluoroscopy images demonstrating the effect of 1 cm advancement on airway site in patient 3 during titration (pre-advancement left, post-advancement right).

Outcome measures

Standard full-night polysomnography was performed (Medilog SAC, Oxford Instruments, Oxon, UK) for screening, baseline and 6 month follow-up. Sleep recordings were scored manually in a standard fashion by the same qualified sleep technician, and scoring was blinded for the sleep technician. The AHI was the average number of respiratory events per hour of sleep. Surgical success was defined as 50% or greater reduction of the AHI and a final AHI of less than 20 (7). For evaluation of snoring, a 10-point, bed-partner evaluated, visual analogue scale (VAS) ranging from zero (no snoring noise) to 10 (extreme snoring: bedpartner has to leave the room) was used as snoring index. The VAS was completed at baseline and 6 month follow-up. Heavy snoring was defined as a snoring index of at least seven. A decrease of 3 points following treatment is considered satisfactory. Sufficient reduction of snoring is considered as a snoring index ≤ 3 (11). Daytime sleepiness was assessed by completing the Epworth Sleepiness Scale (ESS) (12) at baseline and at 6 month follow-up. An ESS score above 10 defined excessive daytime sleepiness. Feasibility was evaluated by procedure-time and occurrence of technical adverse events during the procedure. Safety was evaluated by the occurrence of clinical adverse events.

Tolerability of the procedure was assessed with a pain VAS ranging from 0 (no pain) to 10 (extreme pain) at baseline and during the first 5 consecutive days after the procedure. All patients were given 100 mg tramadol direct post-operatively. After 4 hours, one gift of 1 gram paracetamol was given when asked by the patient. No pain medication was needed from day 1.

Statistical analysis

All data were stored in and analyzed with Microsoft Office Excel 2003 (Microsoft, Redmond, WA, USA). Results were presented as means, ranges and standard deviations. A paired *t* test was used to compare data at screening and baseline, screening and 6 month follow up and baseline and 6 month follow up for PSG sleep variables and to compare data at baseline and 6 month follow up for scores of ESS and Bed Partner Evaluated Snoring. A two-tailed p value of less than 0.05 was considered statistically significant.

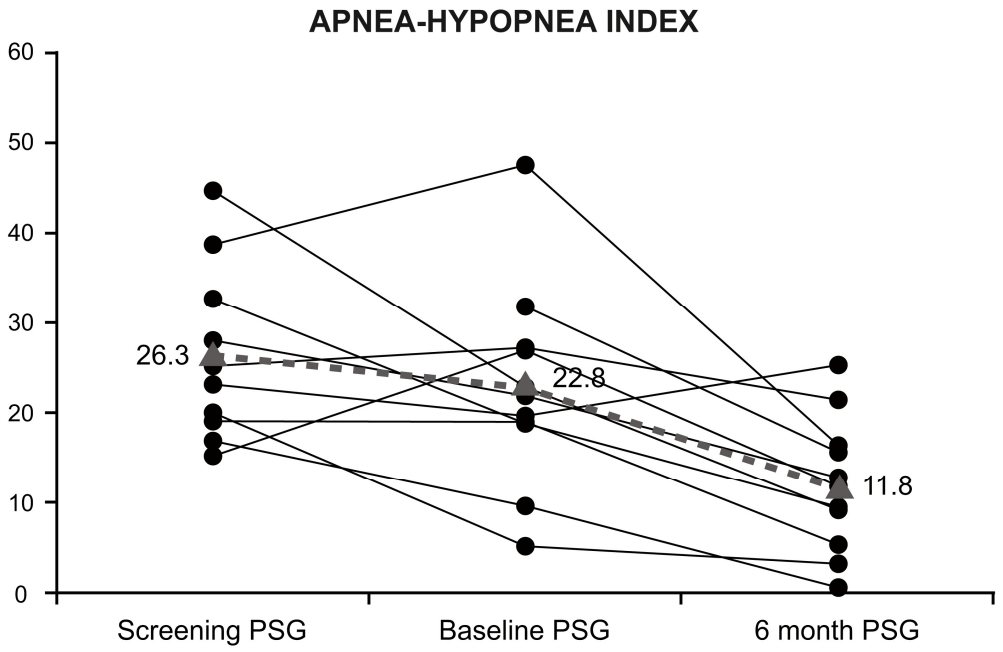
Results

All objective and subjective data were available in the first 10 patients of this trial. There was no significant change in BMI for any of the patients during the study. No patients were lost to follow-up and there were no drop-outs. Screening PSG of patient 9 was performed 2 years before inclusion in the study, which was outside the timeframe of 1 year mentioned in the protocol. This was considered as a violation to the protocol. Therefore this screening PSG was excluded for statistical analysis. All patients returned for at least one titration session and 2 patients returned for a second titration. The average advancement the tissue anchor underwent at the time of titration was 1.4 cm (range 0.25 to 3.5 cm). In one patient the initial advancement of 1.5 cm resulted in significant discomfort so, during the same visit, the advancement was

reduced to 1.0 cm. This degree of advancement was well tolerated by the patient. All other patients have tolerated the advancement procedure well.

Objective outcome

Reduction of the AHI was observed for all patients except one (Table 3). There was no significant difference between screening and baseline AHI (Figure 5). Seven out of ten patients (70%) showed a 50% reduction of the AHI. The average AHI was significantly reduced from 22.8 to 11.8 (P=0.009). This is a reduction of 48%.



p-value	Baseline	6 month follow up
Screening	0.270	0.006
Baseline	–	0.007

FIGURE 5. Apnea-Hypopnea Index (AHI) measured with full-night polysomnography (PSG) at screening, baseline and 6 month follow-up.

TABLE 3: APNEA-HYPOPNEA AND APNEA INDICES OF PATIENTS AT SCREENING, BASELINE AND 6 MONTH FOLLOW-UP AFTER IMPLANTATION USING POLYSOMNOGRAPHY

Patient	Screening AHI	Baseline AHI	Baseline AI	6 month AHI	6 month AI
1	15.3	27.0	3.8	11.6	0.2
2	19.0	18.8	5.7	5.2	0.5
3	17.2	9.6	6.9	0.8	0
4	20.0	5.1	2.5	2.9	–
5	33.1	18.7	0.7	9.3	0.5
6	23.2	19.3	0	25.5	2.5
7	45.0	23.0	0.2	8.9	0.8
8	25.0	27.0	18.7	21.4	14.9
9	–	32.0	0.4	15.5	7.4
10	38.9	47.9	0.6	16.4	3.1

Subjective outcome

Epworth Sleepiness Scale improved from 11.4 at baseline to 7.7 (P=0.094) at 6 month follow-up (Figure 6). This effect was not statistically significant. Four out of the six (67%) patients with excessive daytime sleepiness (EDS) prior to treatment (ESS above 10) had resolution of their hypersomnolence.

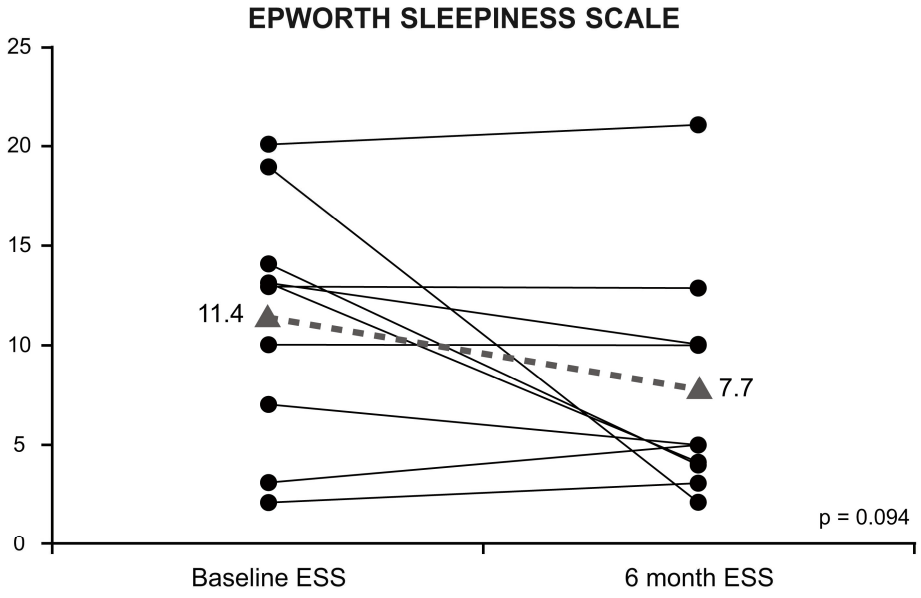


FIGURE 6. Epworth Sleepiness Scale measured at baseline and 6 month follow-up.

Bedpartner evaluated snoring (VAS) improved significantly at 6 month compared to baseline from 7.5 to 3.9 (P=0.005) (Figure 7). Seven out of 10 patients (70%) showed resolution of their socially disturbing snoring.

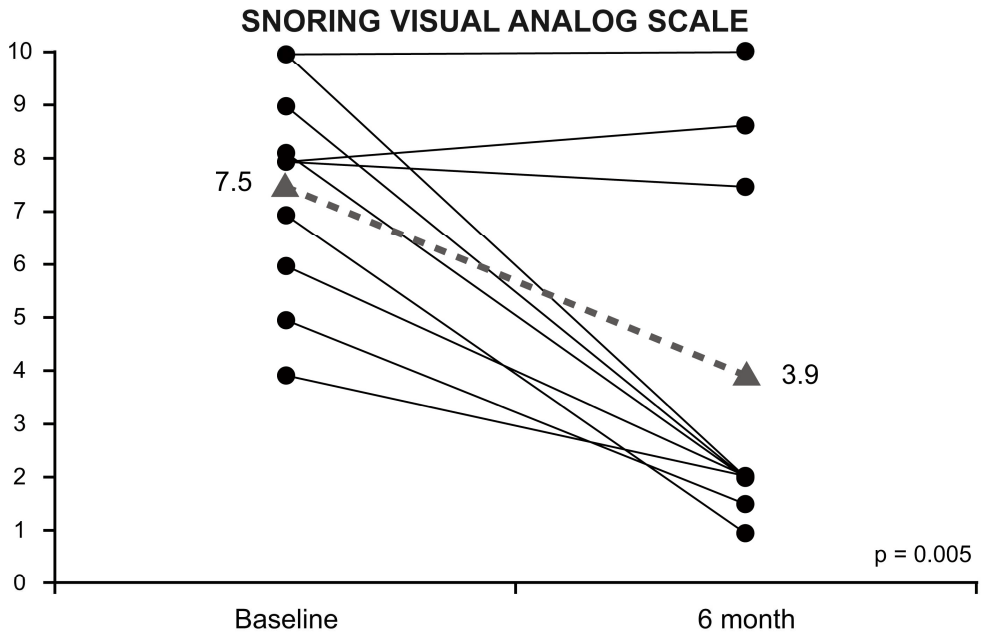


FIGURE 7. Bed partner evaluated snoring measured with a visual analog scale.

Feasibility

The procedure characteristics are shown in table 4.

In four patients (No 2, 3, 4, 7) a detachment of the lingual anchor was noted. After additional testing of the surgeons knot in the laboratory it appeared that this knot was not always reliable and could sometimes fail. We therefore decided to use a modified knot, which was more consistent and reliable. No additional detachments were observed since we used this modified knot. In those four patients a revision procedure was performed. In two patients this revision included recapture of the lingual anchor and adjustment mechanism followed by re-implantation of the complete system. In two patients only the lingual anchor was recaptured followed by a re-implantation. The

originally implanted adjustment mechanism could be used for attachment to the lingual anchor. In two patients, the recapture system was not able to take the lingual anchor out and the lingual anchor had to be removed by dissection in the tongue. In one patient this resulted in a temporary hemiparesis of the tongue, which resolved in two days.

In one patient, the lingual anchor was placed in a sub-optimal location resulting in a poor clinical improvement. Both snoring and daytime sleepiness were unchanged. A lateral view X-ray showed a very shallow position of the lingual anchor that resulted in a limited amount of advancement of the lingual anchor. This patient was followed at 2 months with polysomnography, which showed an increase in the apnea-hypopnea-index (AHI) from 18.8 to 35. This patient elected to have a revision procedure to remove the lingual anchor and implant a new tissue anchor in a more optimal location. This procedure was successfully performed. Subsequently, the patient's 6-month follow-up polysomnography post revision implantation showed an AHI of 5.

TABLE 4. PROCEDURE CHARACTERISTICS

n=10	Average	Range	Standard deviation
Implantation procedure time (min)	74.2	(35 – 179)	44.6
Titration procedure time (min)	24.1	(11 – 58)	15.7
Titration advancement (cm)	1.5	(0.8 – 3.5)	0.8
Patients with two titration procedures	2	–	–

Procedure Safety and Tolerability

All patients were in good health at each of the follow-up visits and except as noted below, there have been no observations of infection, seroma formation, irritation, significant hematoma, inflammation or extrusion or migration of the implant. Patients did not report any significant lasting foreign body sensation or irritation due to the

implant or procedure. None of the patients showed signs of dysphagia or dysphonia during the immediate post-operative period of implantation and titration. Post procedural pain (Figure 8) was limited and lasted only for 1 to 2 days in most patients, and none of the patients required narcotics to manage pain.

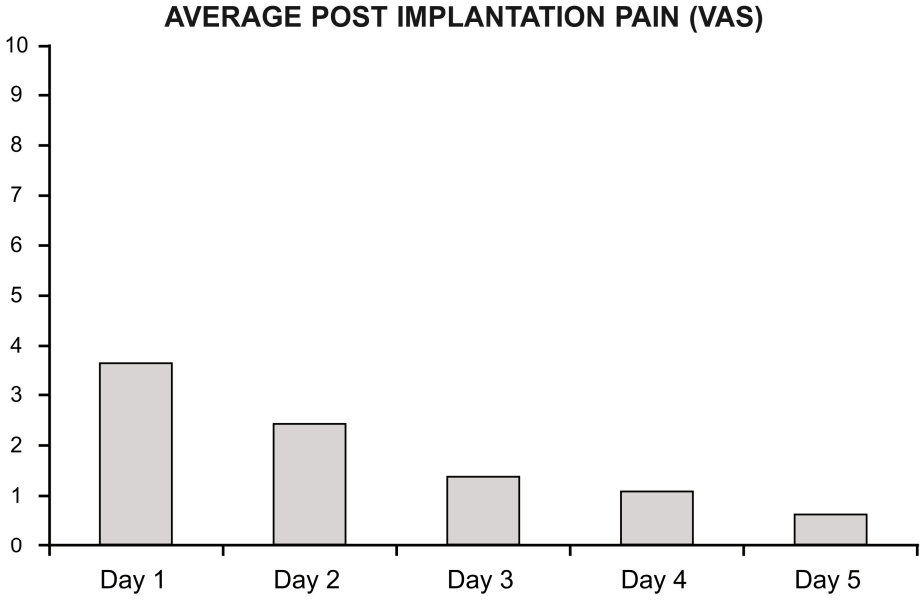


FIGURE 8. Pain visual analog scale measured five consecutive post-operative days.

Wound Healing Complications

In one patient, a 5 mm submental granuloma at the incision spot developed one month after the titration procedure. The granuloma was unsuccessfully managed with IV antibiotics, debridement and hyperbaric oxygen therapy. The implanted device was not implicated in the infection. At the time of this report, the granuloma was decreased to a degree that was not bothersome to the patient. The patient will continue to be monitored.

Discussion

Our group was the first worldwide to implant the Advance™ System in February 2006. This is a prospective, phase 1, feasibility, safety and efficacy study and this paper reports the preliminary results of the first 10 patients with a follow-up time of 6 months. This interim analysis was necessary to determine the further progress of the study.

Since this is a pilot feasibility study, the protocol includes a limited sample of selected patients with tonguebase obstruction.

There are several innovative aspects to the Advance™ System. The clinical effect of the system is achieved by progressively advancing the lingual anchor by using the adjustment mechanism. The forward tension of the lingual anchor can be adjusted during or after the implantation procedure in case the initial clinical effect is insufficient. In the unlikely case the implant has to be removed, the lingual anchor can be recaptured with the use of a recapture system and the bone anchor can be removed by releasing the three fixation screws.

The overall feasibility of the procedure in this stage of the study was moderate. In all of the cases we were able to implant both parts of the implant with success without technical failures during the procedure. The correct positioning of the lingual anchor was achieved by the surgeon's manual guidance in the patient's mouth, and in 9 out of 10 patients aided with the use of fluoroscopy. Although the use of fluoroscopy is not explicitly needed during implantation, our experience is that it is very helpful to get acquainted with the procedure and to find the optimal position of the lingual anchor. Proper positioning of the lingual anchor is crucial for the clinical effect of the Advance™ System. As this is the first experience with the procedure, the optimal position of the lingual anchor has not yet been completely defined. Until we have analyzed the relationship between the position of the lingual anchor and clinical effect, we believe that the best initial position of the lingual anchor is in the base of tongue just behind the circumvallate papillae and close to the dorsal surface of the tongue. The palpability of the trocar via the mouth of the patient allows the surgeon to find this position correctly. In case the position of the lingual anchor is not optimal, the anchor

is withdrawn back into the delivery system and the trocar can be repositioned. Repositioning of the tissue anchor with the trocar did not result in excessive bleeding or post-operative hematoma.

The importance of the adjustability of the device is still uncertain. Obviously, there is a limit on how far the tongue can be advanced and a limit on tolerance of advancement. The limit on how far the tongue can be advanced is mainly determined by the limited length of the tetherline. If the tetherline allows for much advancement, the tolerability becomes the limit. On the other hand it is not sure what happens to the tongue if it is advanced too much. Maybe the intra-oral part of the tongue will be pushed up and creates a palatal obstruction. Limitations of our techniques or ability to identify true type III collapse might be a factor that influences surgical outcome of this procedure.

The tolerability of the implantation procedure was good. Post-operative pain was mild to moderate. With a score of 3.8 on a visual analogue scale of 10 on the first post-operative day, this procedure can be compared with a radiofrequency procedure of the palate (13). There was no foreign body sensation in any of the patients.

Safety issues in this study were mainly related to the initial technical failures of the tetherline fixation. Since we used the modified knot instead of the surgeons knot for fixation, these issues were solved. The reported adverse events in this study were mainly related to the revision procedures because of these detachments. The granulation formation in one patient remained unexplained. Histopathological examination of this granulation did not show foreign body reaction nor infection.

The Advance™ System was able to significantly reduce the apnea-hypopnea-index from 22.8 at baseline to 11.8 at 6 months follow-up. The AHI at screening was used for inclusion in the study, and the baseline and 6 months follow-up AHI was used for evaluation of efficacy. Using different measures for screening and baseline covers the “regression to the mean” effect (14) that is known with polysomnography. Using different measures for screening and baseline limits the effect of night-to-night variability of PSG data. There was no significant difference between screening and baseline evaluation, although the small sample size and the variation weakens the

statistical analysis. The difference between baseline and 6 months follow-up was statistically significant.

This pilot study has important limitations. The strength of the statistical analysis is compromised by the small sample size and the study design (case series). Polysomnography data in general and AHI in particular, show important variation and therefore only limited conclusions can be withdrawn from the efficacy results.

Factors determining clinical efficacy of the Advance™ System include patient selection, site of collapse, location of the tissue anchor and precision of titration. Since this procedure targets the hypopharyngeal segment of the upper airway, patients with clinical evidence of tonguebase collapse were selected. Failure of clinical efficacy could be explained by including patients with palatal collapse or multisegmental collapse. Adjustable titration of the implant is the most crucial aspect of clinical success. With the patient under sedated sleep and using fluoroscopy, titration can be performed with precision and within limits of tolerability. If the clinical effect is insufficient, an additional titration should be performed.

In two patients, the AHI at baseline was below the inclusion criterium used for screening. In one patient, AHI at screening was 17, at baseline 10, and 1 at 6 months follow-up, and in a second patient AHI at screening was 20, at baseline 5, and 3 at 6 months follow-up. Although the baseline AHI in these patients did not necessarily justify surgical treatment, the patient's history and screening AHI was considered as positive for obstructive sleep apnea and therefore the procedure was performed. In both patients the objective outcome measures showed improvement. Subjective improvement was only seen in one of those two patients.

Most of the included patients suffer from moderate to severe OSAS. Only two patients showed an AHI above 30 at baseline. In both cases the AHI was reduced to below 20.

If we use the definition of surgical success (7), 8 out of 10 patients have an AHI below 20. Three of these patients had an AHI below 20 at baseline.

Other techniques with a comparable effect on the tongue are tongue suspension (Repose) and mandibular advancement devices. The difference between the Advance™ System and tongue suspension is its adjustability and low morbidity. Similar as in tongue suspension (Repose), this procedure is performed under general

anesthesia. The manipulation in the patient's pharynx makes this procedure bothersome to the patient when performed under local anaesthesia. Heavy gag reflexes might compromise correct placement of the tissue anchor. A two week period is recommended for healing before putting tension on the tissue anchor. Scarring around the tissue anchor might result in more effective advancement of the tongue during the titration procedure.

Woodson et al report on limited objective improvement after tongue suspension (Repose) (15). In a group of 14 OSA patients, the mean AHI decreased from 35 at baseline to 24 at 2 months follow-up. Epworth Sleepiness Scale significantly decreased from 14 at baseline to 9 at 2 months follow-up. Snoring decreased significantly after 2 months but was still bothersome to the partner. Three of the 14 (21%) patients reached the following definition of surgical success: 50 % reduction in AHI and AHI < 15. Post-operative complications were seen in 15% of cases.

The differences in efficacy between tongue suspension (Repose) and the Advance™ System is probably due to the adjustability of the system. With tongue suspension, once the knot forming the suspension suture is tied, no more modification to the advancement of the tongue can be made. This necessitates that the surgeon correctly judges the amount of advancement during the procedure. Since the procedure is performed under general anesthesia with intubation, complete relaxation of the tongue may hinder a correct judgment of the amount of advancement necessary for a particular patient. With the Advance™ System, tongue advancement is not attempted during implantation but two weeks after implantation. Adjustment of the device under local anesthesia with sedation allows for the advancement of the tongue in a controlled way and to an amount optimized for each particular patient. The clinical effect can be measured during the procedure by attenuation of snoring and the behavior of the upper airway visible with fluoroscopy or endoscopy, and after the procedure with subjective and objective measures as discussed earlier in this paper. If subjective and/or objective measures show insufficient clinical response, further titration can be performed.

Some Mandibular Advancement Devices (MAD) have the ability of adjustment. The overall efficacy of MAD in patients with moderate to severe OSA varies between 14 and 61%, whereas for mild to moderate OSA the efficacy varies between 57 and 81%

(16). Increased amounts of mandibular protrusion produce greater reduction in respiratory events. Overall patient compliance with MAD is 71% at 1 year and this compliance decreases with duration of use (16).

Once the Advance™ System is implanted and titrated, the clinical effect is continuously present. There is no issue with compliance or side effects during treatment. The tension on the tongue caused by the device is enough to prevent the tongue from obstructing the upper airway during sleep, but not enough to cause side effects like dysphagia or dysphonia while awake. The achieved effect is present during total sleep time while in MAD or CPAP treatment the effect is only present during those hours of sleep where the treatment is tolerated by the patient. In a prospective study of CPAP adherence, only 46% of patients were using their CPAP for at least 4 hours per night on 70% of the nights (17). Adherence to CPAP is overestimated by most patients. Therefore further study of the Advance™ System is needed to investigate efficacy before it could be considered an alternative treatment in those patients with poor adherence or tolerability of CPAP.

Conclusion

The Advance™ System reduces AHI with 48%. Seventy percent of the patients show a 50% reduction of AHI. Complication rate and side effects were mainly due to technical learning curve. Feasibility and safety are satisfactory. This is a novel technology applied for the first time worldwide for surgical treatment of obstructive sleep apnea in patients with type 3 collapse. Patients who are intolerant to or seeking an alternative for CPAP treatment might benefit from this procedure, although further study is needed to investigate efficacy of this procedure.

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Chapter 7

Adjustable tongue advancement for obstructive sleep apnea: position of the tissue anchor versus outcome

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Introduction

Obstructive sleep apnea syndrome(OSAS) is caused by partial or complete collapse of the upper airway during sleep. There are different patterns of collapse, depending on the level in the upper airway where the collapse occurs. Retropalatal collapse and retrolingual collapse are the most common sites of upper airway obstruction. Planning for surgical treatment of OSAS starts with determining the level of obstruction (1) in order to select the patient for a site specific treatment. Palatal obstruction can be treated by a wide range of procedures (2). Procedures which address the retrolingual segment of the upper airway are mostly invasive accompanied by important morbidity and lack evidence based efficacy (3).

Continuous positive airway pressure (CPAP) is the first choise treatment for patients with moderate to severe OSAS (4). An important group of patients are intolerant to this treatment or show a lack of adherence (5). Multilevel obstruction (both retropalatal and retrolingual) and retrolingual obstruction in particular play an important role in patients with moderate to severe OSAS (6). Innovative research for new procedures addressing the retrolingual segment of the upper airway is therefore justified.

Adjustable tongue advancement with the use of the Advance System is a novel surgical procedure which addresses the tongue base by implanting a tissue anchor in the tonguebase and an adjustment spool at the lower rim of the mandible. The technique and preliminary results of this procedure were recently published by our group (7). A significant reduction of the apnea-hypopnea-index (AHI) was achieved by advancing the tongue with this novel technique.

The position of the tissue anchor in the tongue base at the time of implantation was determined by the surgeon with the use of manual palpation intra-orally and fluoroscopy. Since we were the first to perform this procedure in humans, no information about the optimal position of the tissue anchor was available. It could be argued that the tissue anchor should be close to the dorsum of the tongue base in order to have a maximum of tetherline length for advancement, but this position could result in formation of a dimple at the tonguebase level, leading to insufficient advancement.

On the other hand, a certain distance from the dorsum could result in scar formation around the tissue anchor, which could enhance the total amount of tongue advancement but might result in a short tetherline length limiting the amount of advancement at titration.
The aim of this study was to evaluate the effect of variable positions of the tissue anchor in the tonguebase on the objective outcome measures, being the post-operative apnea-hypopnea-index (AHI).

Material and method

In a retrospective study the effect of variable positions of the tissue anchor in the tongue base at the time of implantation was compared with the improvement of AHI six months after titration.
From February 2006 till April 2007, 23 patients were implanted with the Advance System in a prospective, multicenter, single-arm pilot study at the University Hospital Antwerp in Belgium (14 patients) and at the University Hospital Mannheim in Germany (9 patients). The technique of implantation and titration of the Advance System was previously described (7).

During the implantation procedure under general anaesthesia, the tonguebase was approached by a trocar in a cannula (figure 1). After removing the trocar and leaving the cannula in place, the tissue anchor was delivered to the tonguebase via the cannula (figure 2). After delivering the tissue anchor, the position was determined by oral palpation and with fluoroscopy. The systematic use of fluoroscopy was only performed in Antwerp and not in Mannheim, and therefore the available data origin from the patients implanted in Antwerp. Fluoroscopy was used at implantation in all the 14 patients and images captured and printed. X-rays at 2 months and/or 6 months follow-up visits were taken depending on the clinical status of the patient and/or the PSG outcome (figure 3).

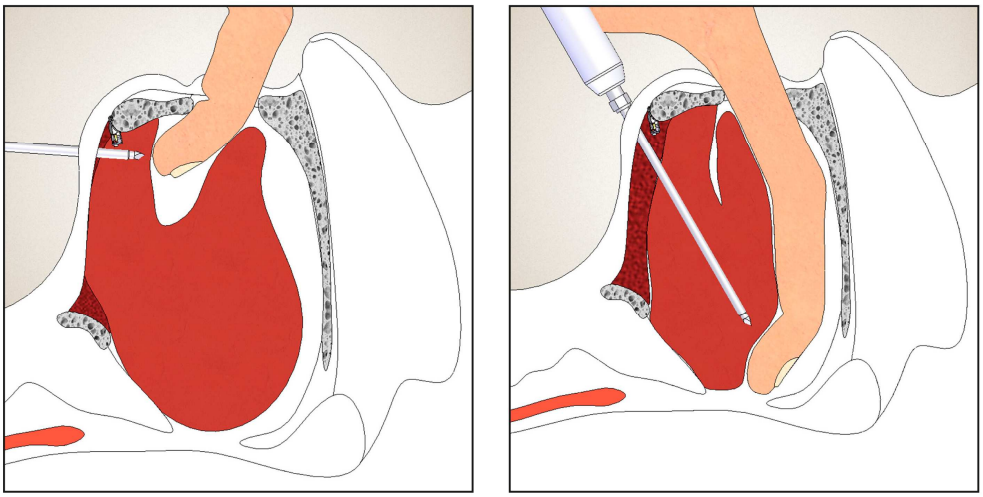

FIGURE 1. Introduction of trocar. Left: Introduction of trocar/cannula into the genioglossus using digital palpation. Right: Positioning trocar at base of tongue approximately at the circumvallate papillae.

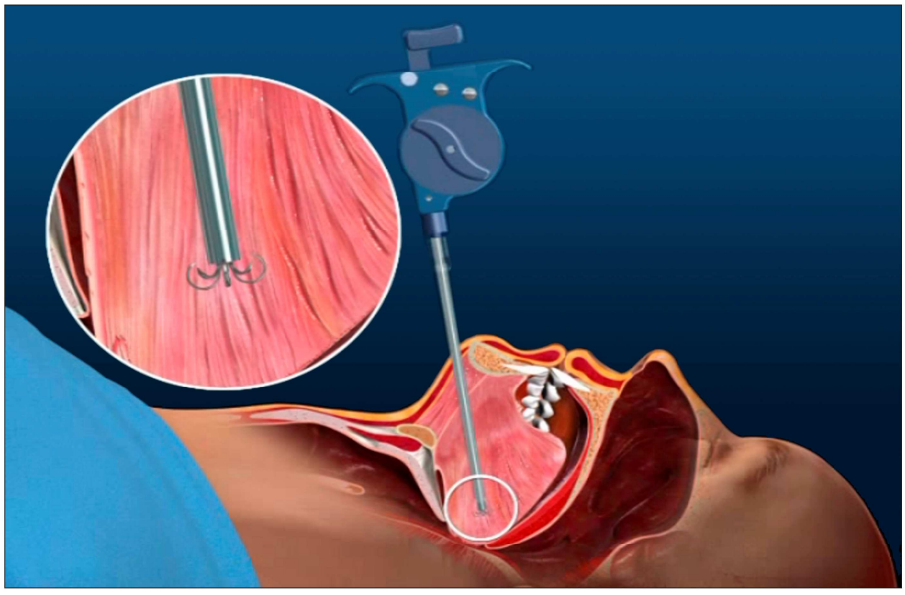

FIGURE 2. Delivery of the tissue anchor into the tongue with the delivery system

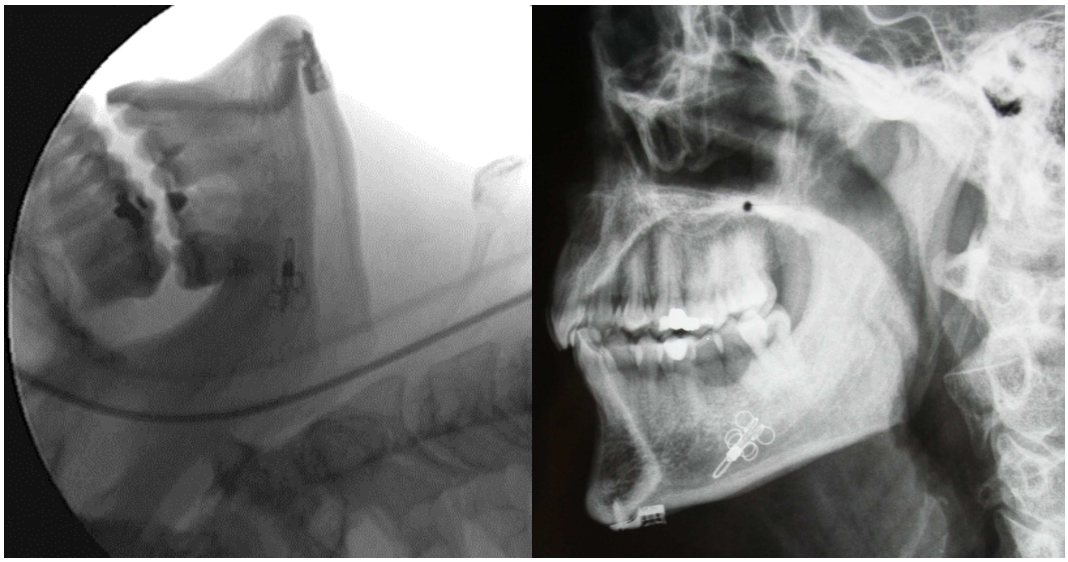

Figure 3. Patient A10. Left: position of tissue anchor at implantation with fluoroscopy. Right: tissue anchor 3 months post-op with X-ray.

The position of the tissue anchor on the fluoroscopy image and on the post-op X-ray was projected on a grid which was placed on an X-ray of a random patient in this study. This X-ray was used as a model for the analysis of the positioning study (figure 4). A red line was drawn at the spot were the tonguebase was projected, and this line was used as baseline for measurement for the distance between the tonguebase and the tissue anchor. The baseline of the grid was positioned at the lower rim of the mandible and was used as baseline for measurement of the distance between the tissue anchor and the level in the tonguebase.

The position of the tissue anchor was determined by measuring the distance from the dorsal side of the tongue to the proximal end of the tissue anchor, and the distance from the lower rim of the mandible to the proximal end of the tissue anchor.

After drawing the different positions of the tissue anchors on the grip (figure 4), the outcome in AHI was compared with the position of the tissue anchor at implantation. Successful outcome was defined as 50% reduction of AHI after advancement.

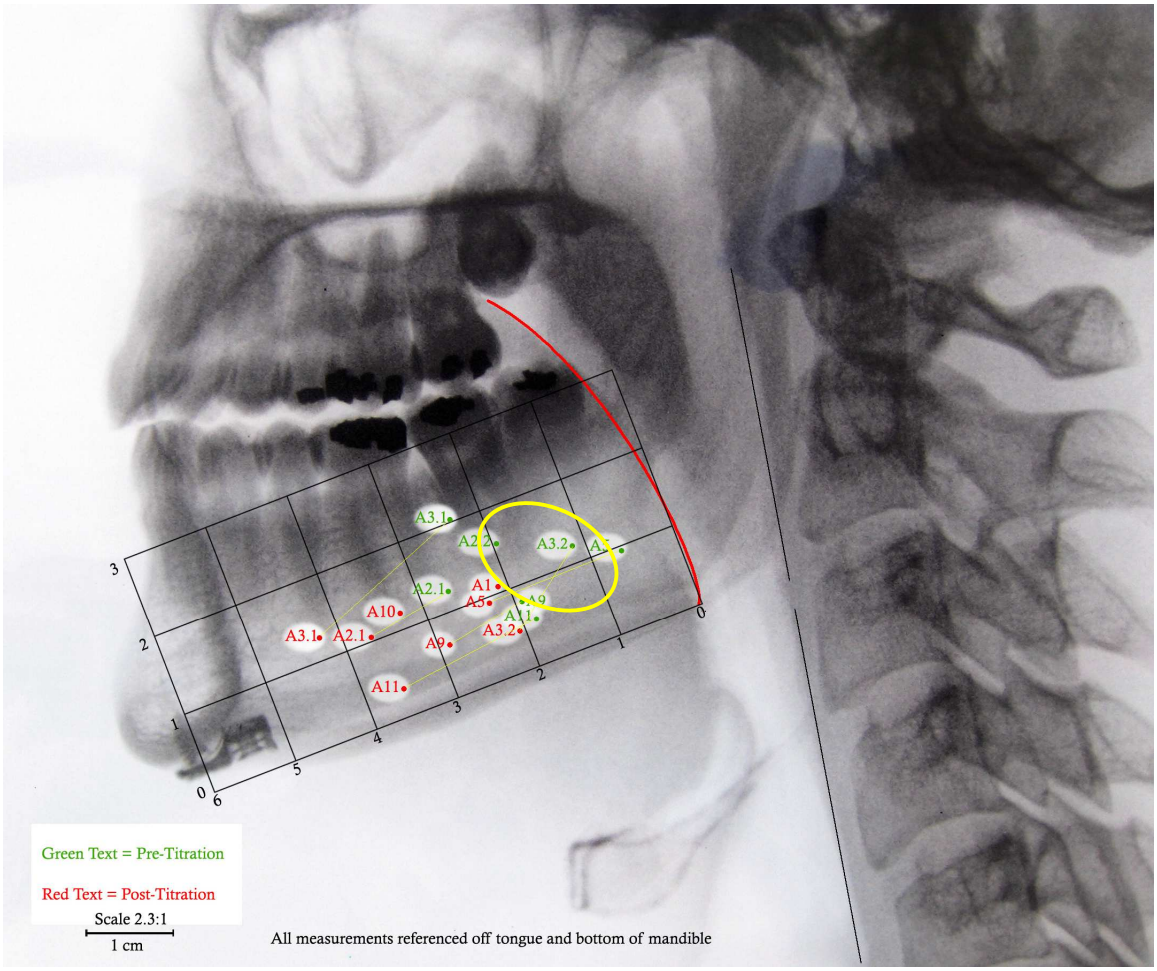

Figure 4. Positions of tissue anchor at implantation (green) and post titration (red). The “target position” is marked as a yellow circle. The red line is the dorsum of the tongue base.

Results

From the 14 patients, both fluoroscopy images at implantation and X-ray images at 6 months follow-up visits, were available in 5 patients (A2, A3, A5, A9 and A11). Patient 2 was re-implanted because the tissue anchor was implanted not close enough to the dorsum of the tongue. At the titration procedure, a maximum of titration was achieved but this was not sufficient to result in clinical improvement. Therefore it was decided to re-implant the tissue anchor closer to the dorsum of the tongue. After re-implantation, no follow-up X-ray was available. Patient 3 was re-implanted because of a detachment of the tissue anchor. The data of both first and second implantation were available for this study. In the other patients, in spite of using fluoroscopy at

implantation, no images were stored or the quality of the images was insufficient for analysis.

The data of the tissue anchors position in the tongue base are presented in table 1.

Baseline polysomnographic data were available in all patients. Two months follow-up PSG data were not available for revision implantation in patient A2 and for patient A11. Six months follow-up PSG data were not available in patient A2 and A3, since these patients were re-implanted. The data of the AHI measured by full-night polysomnography at baseline, at 2 months follow-up and at 6 months follow-up are presented at table 2. The position of the tissue anchor in the tongue base at implantation and after advancement are presented in figure 4.

Table1. Position measurements of the tissue anchor.

Pt. ID	Anchor Position (distance from feature, cm)			
	Implantation		Advanced	
	Dorsum	Mandible line	Dorsum	Mandible line
A1			2,1	1,1
A2,1	2,7	1,3	*3,7*	*1*
A2,2	*2*	2,6		
A3,1	2,4	2	4,2	1,2
A3,2	1,2	1,2	2	0,5
A5	0,7	1	2,3	1
A9	1,9	0,8	2,9	0,7
A10			3,3	1,2
A11	1,9	0,5	3,6	0,3

Table 2. Data of apnea-hypopnea-index.

Pt. ID	Baseline	2 months	6 months
	AHI	AHI	AHI
A1	27	24	12
A2,1	19	15	
A2,2	19		5
A3,1	10	4	
A3,2	10	5	1
A5	19	16	9
A9	32	19	16
A10	22	6	13
A11	19		9

Discussion

Patient A2 has two data points: initial implantation and re-implantation. Tissue anchor position A2.1 showed a decrease of the AHI from 19 to 15 at two months follow-up. After re-implantation, the tissue anchor position A2.2 showed a decrease to 5 at 6 months follow-up. Position A2.2 was closer to the dorsum of the tongue and apparently a better position than the original position.

Patient A3 has two data points: initial implantation and re-implantation. Tissue anchor position A3.1 showed a decrease of the AHI from 10 to 4 at two months follow-up. After re-implantation, the tissue anchor position A3.2 showed a decrease to 1 at six monts follow-up. Position A3.2 was closer to the dorsum of the tongue and lower in the tongue base and apparently a better position than the original position.

Tissue anchor position A5 showed a decrease in AHI from 19 to 9 at six months follow-up. This position is close to the dorsum and low in the tongue base. This seems to be an effective position.

Tissue anchor position A9 showed a decrease in AHI from 32 to 16 at six months follow-up.

This position is far from the dorsum and low in the tongue base. This seems to be an effective position.

Tissue anchor position A11 showed a decrease in AHI from 19 to 9 at six months follow-up.

This position is far from the dorsum and low in the tongue base. This seems to be an effective position.

Tissue anchor position A1 and A10 are post-titration positions. Their orinigal position at implantation can only be speculated. In both patients, AHI dropped with more then 50%.

Successful positions were A2.2, A3.2, A5, A9 and A11. Unsuccessful positions were A2.1 and A3.1.

If we look at the positions of the tissue anchors at the time of implantation of those patients with successful outcome, we could argue that the optimal position is situated

1-2 cm away from the dorsum of the tongue base and 1-1.5 cm above the lower rim of the mandible. This “target area” is drawn as a circle on the grid (figure 4).
The initial position of the tissue anchor in patients A1 and A10 was not known since fluoroscopy image at implantation was not available. However the position after advancement presumes that the initial position of patient A1 was probably situated in this target area. The original position of patient A10 is difficult to presume.

Successful improvement was defined as 50% reduction in AHI. The definition of surgical success according to Sher et al. (8) suggests a 50% reduction in AHI and a post-operative AHI below 20. Since we were interested those patients who showed significant reduction in AHI, we excluded the latter criterium in this analysis. An AHI below 20 does not necessarily mean a significant reduction in AHI.

This study has important limitations. The sample size is small and therefore only limited conclusions can be made from this study.
Determination of the position of the tissue anchor on the fluoroscopy image was slightly compromised by the fact that the patient was in a recumbent position and intubated during the procedure. The intubation tube might influence the natural position of the tongue. Measurements of post-advancement positions were performed on X-rays taken in awake patients in an upright position. In these images the tongue appears to be in a more natural position. Comparing positions in two different types of images might have influenced the results of this study.

We argue that the “target position” of the tissue anchor is relatively close to the dorsum of the surface of the tonguebase because this creates a longer distance between the adjustment spool and the tissue anchor and therefore more space for advancement. If the tissue anchor is implanted in a shallow position, advancement could be limited and therefore compromise clinical outcome.
Implanting the tissue anchor too close to the surface of the tongue base could result in perforating the dorsum of the tongue and exposure of the implant in the (non-sterile) oral cavity. Positioning the tissue anchor less than 1 cm to the surface would result in

dimple formation while advancing. This could result in an advancement of the tongue base in the center but incomplete advancement at the edges of the tongue base.
The results of this study might be of interest in the further development of implants for tongue advancement.

Conclusion

Adjustable tongue advancement is a novel technique for surgical treatment of obstructive sleep apnea. The implantation procedure is facilitated by the use of fluoroscopy. Using fluoroscopy and X-ray images, the optimal position of the tissue anchor, called the “target position”, was determined to be 1-2 cm close to the surface of the dorsum of the tonguebase and 1-1.5 cm above the lower rim of the mandible.

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Chapter **8**

Summary and conclusions

Samenvatting en conclusies

Six aims were formulated in this thesis:

1. To focus on the present knowledge of diagnosis and treatment of obstructive sleep apnea syndrome (chapter 2).
2. To evaluate the role of drug-induced sleep endoscopy as a diagnostic tool to identify tonguebase and hypopharyngeal collapse of the upper airway (chapter 3).
3. To evaluate feasibility, safety and efficacy of hyoid expansion as a new procedure for obstructive sleep apnea in patients with hypopharyngeal lateral wall collapse (chapter 4).
4. To evaluate feasibility, safety and histology of an adjustable tongue anchor for the treatment of obstructive sleep apnea in an animal model (chapter 5).
5. To evaluate feasibility, safety and efficacy of adjustable tongue advancement as an innovative procedure for obstructive sleep apnea in patients with tonguebase collapse (chapter 6).
6. To evaluate the effect of the position of the tongue anchor on the objective outcome measures in patients treated with adjustable tongue advancement (chapter 7).

Aim 1.

Chapter 2 gives an overview of the diagnostic work-up and current treatment options for OSAS. Diagnosis of OSAS is a combination of the medical history, the clinical examination and sleep registration. In order to evaluate the site of obstruction in the UA, specific investigation techniques are available which allow for better patient selection for specific (surgical) treatment. Sleep endoscopy seems to be preferable because of its simplicity, low costs, reliability, safety and specificity.

Continuous positive airway pressure (CPAP) is the gold standard treatment for OSA. Other (non-CPAP) treatments should be considered in three situations: First, individuals with clearly reversible causes of OSAS (anatomical abnormalities) should be considered for surgery. Second, individuals who have failed or refuse CPAP

treatment should be considered for other approaches (oral appliances or upper airway surgery). Third, treatment of mild OSAS is a subject of debate. Specific surgical treatment options are described and their specific indications discussed.
Surgical treatment of the hypopharynx lacks evidence based efficacy and has substantial morbidity. Patient selection for hypopharyngeal obstruction is controversial and much debated.

Aim 2.

Many specific methods for evaluation of the UA are available with their specific advantages and disadvantages. In chapter 3 the role of sleep endoscopy is evaluated in the selection of patients with hypopharyngeal or tonguebase obstruction. The majority of patients with OSAS seem to have multilevel obstruction (both palatal and hypopharyngeal), and the minority of patients present pure tonguebase or hypopharyngeal collapse. The technique of sleep endoscopy is simple and safe, and allows for evaluation of site and pattern of obstruction. No complications were observed. Site-specific (surgical and non-surgical) treatment could be offered to the patient after sleep endoscopy.

Aim 3.

The role of the lateral hypopharyngeal walls in UA collapse is controversial. Specific surgical treatment to correct hypopharyngeal lateral wall collapse is almost inexistent. The anatomical position of the hyoid bone makes it an ideal substrate for widening the hypopharyngeal airway space and stabilize the lateral walls. In a prospective multicenter study, the feasibility, safety and efficacy of a hyoid expansion implant was evaluated in 26 patients with OSAS and hypopharyngeal lateral wall collapse. Although there were responders and non-responders, no statistical objective improvement of apnea-hypopnea-index (AHI) was observed. However, there was significant improvement of subjective measures like snoring and daytime sleepiness. According to the findings in this study, hyoid expansion using the described technique and implant is not a valid treatment option for patients with OSAS.

Aim 4.

Treatment of tonguebase obstruction in OSAS patients is challenging. Present procedures like radiofrequency ablation of the tonguebase, tongue suspension or partial tonguebase resection, are ineffective, invasive and have substantial morbidity.

A novel concept of adjustable tongue advancement was studied for feasibility, safety and histology in an animal model. The implantation of a two-fold tongue implant (tissue anchor and bone anchor), and the retrieval procedure, could be performed uneventfully in all cases. Some minor complications, related to this specific animal model, were observed and could be successfully managed. Histological evaluation of the tissue anchor showed normal incapsulation with only minor signs of inflammation. Inflammation decreased over time and no substantial foreign body reaction was observed. Histological evaluation of the bone anchor showed good osseo-integration of the fixation screws and bone-regrowth at the bone-implant interface. The findings of this study resulted in the development of an investigational tongue implant suitable for human implantation.

Aim 5.

A novel procedure for adjustable tongue advancement for the treatment of OSAS was studied in a prospective multicenter study. This pilot study reports on data concerning feasibility, safety and efficacy in the first 10 patients that were treated with this technique. The implant procedure could be performed uneventfully in all patients. No significant complications could be observed in the post operative period. Patient-evaluated morbidity was low.

A significant improvement of both objective and subjective measures was observed. Apnea-hypopnea-index decreased almost 50% (from 22.8 to 11.8). Significant improvement of snoring and daytime sleepiness was also observed. This novel treatment needs further study, as the preliminary results are promising for treatment of CPAP intolerant patients with mild to moderate OSAS based on tonguebase collapse.

Aim 6.

Adjustable tongue advancement is a novel technique for the treatment of OSAS. Satisfactory clinical results were observed in a pilot study. In order to improve the results, the effect of the position of the tongue anchor on objective outcome measures (AHI) was retrospectively studied in 5 patients. The position of the tissue anchor at implantation using fluoroscopy images and the position of the tissue anchor after titration, were linked with change in post-operative AHI. The data of this study support the idea that the tissue anchor should be placed close to the dorsum of the tonguebase halfway between the level of the palate and the epiglottis.

Zes doelstellingen werden geformuleerd in deze thesis:

1. Het uiteenzetten van de huidige kennis over diagnostiek en behandeling van obstructief slaap apneu syndroom (hoofdstuk 2).
2. Het evalueren van de rol van medicamenteus-geinduceerde slaapendoscopie als een diagnostisch onderzoek om hypofaryngeale en tongbasis collaps van de bovenste luchtweg te identificeren (hoofdstuk 3).
3. Het evalueren van de uitvoerbaarheid, de veiligheid en het effect van hyoid verbreding als een nieuwe behandelingsoptie voor obstructief slaap apneu syndroom bij patienten met hypofaryngeale laterale wand collaps van de bovenste luchtweg (hoofdstuk 4).
4. Het evalueren van de uitvoerbaarheid, de veiligheid en histologie van een aanpasbaar tonganker voor de behandeling van obstructief slaap apneu syndroom in een diermodel (hoofdstuk 5).
5. Het evalueren van de uitvoerbaarheid, de veiligheid en het effect van aanpasbare tongverankering als een innovatieve ingreep voor obstructief slaap apneu syndroom bij patienten met tongbasis collaps van de bovenste luchtweg (hoofdstuk 6).
6. Het evalueren van het effect van de positie van het tonganker op de objectieve resultaten bij patienten behandeld met aanpasbare tongverankering wegens obstructief slaap apneu syndroom (hoofdstuk 7).

Doelstelling 1.

Hoofdstuk 2 geeft een overzicht van de diagnostiek en de meest gangbare behandelingsmogelijkheden voor OSAS. De diagnose van OSAS wordt gesteld door een combinatie van anamnese, klinisch onderzoek en slaapregistratie. Voor het opsporen van de plaats van obstructie in de bovenste luchtweg (BLW) staan er verschillende onderzoekstechnieken ter beschikking die het mogelijk maken om patienten beter te selecteren voor het uitvoeren van plaats-specifieke (heelkundige) behandelingen. Een voorkeur gaat uit naar slaapendoscopie omwille van de voordelen:

eenvoudig uit te voeren, betrouwbaar en reproduceerbaar, goedkoop, veilig en specifiek.

Continue positieve luchtwegdruk (CPAP) is de gouden standaard behandeling voor OSAS. Andere (niet-CPAP) behandelingen dienen overwogen te worden in 3 verschillende situaties: ten eerst: bij patienten met duidelijk corrigeerbare anatomische afwijkingen van de BLW dient heelkunde overwogen te worden. Ten tweede: patienten die intolerant zijn voor CPAP of deze behandeling weigeren dienen overwogen te worden voor andere behandelingen (mondstukjes of heelkunde). Ten derde: de behandeling van mild OSAS is een onderwerp van discussie. Bij deze patienten dienen eerst conservatieve maatregelen getroffen te worden, zoals gewichtsreductie, behandeling van neusobstructie, vermijden van spierrelaxerende medicatie inclusief alcohol, slaap-positie training en optimale slaap hygiene.

Specifieke heelkundige behandelingsmethoden worden beschreven met hun specifieke indicaties. Voor de heelkundige behandeling van de hypofarynx ontbreekt er evidence based bewijs, en deze heelkunde heeft belangrijke morbiditeit. Over patienten selectie voor hypofaryngeale obstructie bestaat geen concensus.

Doelstelling 2.

Er zijn verschillende methoden beschikbaar voor het evalueren van de BL, elk met zijn specifieke voor- en nadelen. In hoofdstuk 3 wordt de rol van medicamenteus-geinduceerde slaapendoscopie geëvalueerd voor het selecteren van patienten met hypofaryngeale collaps van de BLW. De meerderheid van de patienten met OSAS vertoont multi-level obstructie (zowel palatale als tongbasis collaps), en de minderheid vertoont enkel tongbasis collaps. Slaapendoscopie is technisch eenvoudig en veilig en het stelt de onderzoeker in staat het type en het patroon van collaps van de BLW te evalueren. Er traden geen complicaties op. Op basis van de slaapendoscopie kon aan de patient een plaats-specifiek behandelingsadvies gegeven worden.

Doelstelling 3.

De rol van laterale wand collaps van de BLW is controversieel. Er bestaat geen specifieke heelkundige behandeling om laterale wand collaps te behandelen. De

anatomische positie van het hyoid is ideaal om de hypofarynx te verbreden en de laterale wand te stabiliseren.

De uitvoerbaarheid, veiligheid en het effect van hyoid verbreding met behulp van een implant werd in een prospectieve multicenter studie geëvalueerd in 26 patienten met OSAS en hypofaryngeale laterale wand collaps. Er kon geen statistisch significante verbetering van apneu-hypopneu-index (AHI) worden vastgesteld. Zowel het snurken en de slaperigheid overdag waren wel significant verbeterd. De resultaten van deze studie tonen aan dat de gebruikte techniek van hyoid verbreding bij deze groep patienten geen valabele behandeling is voor OSAS.

Doelstelling 4.

De behandeling van tongbasis collaps in OSAS patienten is een uitdaging. De huidige technieken zoals radiofrequentie ablatie van de tongbasis, tongophanging of partiele tongbasis resectie zijn weinig efficient, invasief en hebben belangrijke morbiditeit. Een nieuw concept van aanpasbare tongverankering werd op een diermodel bestudeerd op uitvoerbaarheid, veiligheid en histology. De implantatie van het tweevoudig implant (tonganker en botanker), en de procedure om het implant te verwijderen, konden in alle gevallen zonder problemen uitgevoerd worden. Er traden enkele minieme complicaties op die gerelateerd waren aan dit specifiek diermodel. Deze complicaties konden behandeld worden. De histologische evaluatie van het tonganker toonde normale inkapseling gepaard gaande met minieme inflammatie. De inflammatie verminderde met de tijd en er werd geen belangrijke vreemdlichaam reactie waargenomen. Histologische evaluatie van het botanker toonde goede osteo-integratie van de fixatie schroeven in de mandibula en botnieuwvorming tussen het botanker en de mandibula. De bevindingen van deze studie hebben geleid tot de ontwikkeling van een veilig tong implant dat geschikt is voor implantatie bij de mens.

Doelstelling 5.

In een prospectieve multicenter studie werd een innovatieve behandeling voor aanpasbare tongverankering bestudeerd. Deze piloot studie rapporteert de gegevens over de uitvoerbaarheid, de veiligheid en het effect van deze ingreep bij de eerste 10

patienten die met deze techniek behandeld werden. De implantatie kon in alle patienten succesvol uitgevoerd worden. Er werden geen complicaties waargenomen in de per- en postoperatieve periode. De morbiditeit werd door de patienten als laag gescoord. Er werd een significante verbetering van zowel objectieve als subjectieve parameters waargenomen. De apneu-hypopneu-index verminderde met 50% (van 22.8 naar 11.8). Tevens trad er een significante verbetering op van snurken en slaperigheid overdag. Gezien de hoopgevende resultaten van deze innovatieve behandeling dient deze verder bestudeerd en geoptimaliseerd te worden.

Doelstelling 6.

Aanpasbare tongverankering is een innovatieve techniek voor de behandeling van OSAS. Er werden bevredigende resultaten gerapporteerd in een piloot studie. Om de resultaten te optimaliseren werd het effect van de plaats van het tonganker op de objectieve resultaten (AHI) bestudeerd bij 5 patienten. De positie van het tonganker tijdens implantatie en na titratie, vastgelegd met röntgenscopie of röntgenfoto, werden gekoppeld aan de verandering van AHI. De gegevens van deze studie doen vermoeden dat de optimale positie van het tonganker dicht tegen het oppervlak van de tong ligt, en dit halverwege het niveau van de uvula en de epiglottis.

Future perspectives

Surgery for OSAS aims for decreasing critical closing pressure of the collapsible segment of the upper airway. A proper and reliable diagnostic work-up should result in a better understanding of the site of collapse of the upper airway. Using sleep endoscopy or multi-sensor pressure measurements, it is shown that the majority of patients show multilevel collapse of the upper airway. In order to improve patient selection for upper airway surgery and inter-observer variability, the methodology of sleep endoscopy needs an optimal and uniform standardisation and classification. Classification should not only focus on site of collapse but also on type of collapse.

Aero-engineering is a new way of looking at the upper airway. Functional imaging using computational fluid dynamics might help to understand the site and pattern of collapse in the upper airway. Comparison of functional imaging and sleep endoscopy is ongoing.

After performing a proper diagnostic work-up, treatment of the OSAS patient should be custom-made and well adapted to the specific problems and causes in the particular patient. In most patients with mild to severe OSAS, a multilevel surgical treatment is therefore appropriate. A combination of a palatal procedure and a tonguebase- or hypopharyngeal procedure, in one or multiple stages, will probably result in better treatment outcome than a unilevel approach. Invasive palatal procedures, like UPPP, are highly effective in well selected patients, and should not be avoided in spite of the tendency towards minimal invasive (and sometimes less efficient) palatal procedures.

Further innovative research for the treatment of tonguebase- and hypopharyngeal collapse is needed, with the use of implants that are reliable and not susceptible for technical failure. The use of eminent and biocompatible material is of utmost importance. Titratability of such implants seems to be the key to superior results.

List of publications

List of publications

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