Evaluation of surgical methods for sleep apnea and snoring

Thorbjörn Holmlund

Department of Clinical Sciences,
Otorhinolaryngology, Umeå University, Umeå,
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Dedication

To my wife, Lena,
and our children,
Ida, Olof and Jacob

Laugh and the world laughs with you, snore and you sleep alone

Anthony Burgess (1917-1993)

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Abstract

Background

Snoring and obstructive sleep apnea are both common disorders with a number of negative health effects, such as daytime sleepiness, hypertension, cardiovascular diseases and swallowing dysfunction. Reduced airway in the oropharynx, including the tonsils, uvula and soft palate, is the most common cause of snoring and obstructive sleep apnea. It is believed that snoring can progress to obstructive sleep apnea due to the trauma caused by vibrations in the pharyngeal tissues. Impairment of neuromuscular components may contribute to an upper airway collapse. Snoring is also associated with deterioration in swallowing function. Continuous positive airway pressure and oral appliances are both effective as treatment for snoring and obstructive sleep apnea, but not all patients are able to comply or adapt to these methods. For this reason, surgery has an important role to play. The safety and efficacy of surgery have been questioned and there has been a lack of studies in the field. To date, there are few prospective, randomized, controlled studies analyzing the outcome of the surgical treatment of snoring and obstructive sleep apnea in adults. The overall aim of the present PhD thesis was therefore to investigate effects and side effects of some common surgical methods in adults, including uvulopalatopharyngoplasty, radiofrequency surgery of the soft palate and tonsillectomy. Furthermore, we will investigate the morphology and cytoarchitecture of upper airway muscles and nerves in normal subjects. This study will form the basis for our future projects to investigate the effect of snoring and sleep apnea on muscle and nerve tissue. This hopefully helps us to formulate new treatment strategies in future.

Methods and Results

In Paper 1, a retrospective database study, we investigated the frequency of serious complications, including death, of surgery for the treatment of snoring and sleep apnea. All Swedish adults who were treated surgically because of snoring or sleep apnea from January 1997 to December 2005 were identified in the National Patient Register. None of the surgically treated patients died in the peri- and postoperative period. Severe complications, mainly bleeding and infection, were recorded in 37.1 of 1,000 patients treated with uvulopalatopharyngoplasty, in 5.6 of 1,000 patients after uvulopalatoplasty and in 8.8 of 1,000 patients after nasal surgery.

In Paper 2, we evaluated the effect of radiofrequency surgery of the soft palate on daytime sleepiness in 35 snoring men with mild or no sleep apnea. The study was designed as a randomized, controlled trial. Patients were randomized to either radiofrequency or sham surgery of the soft palate. Thirty-two of 35 patients, 19 of 20 in the radiofrequency surgery group and 13 of 15 in the sham surgery group, completed the study. No differences between the two groups in relation to the Epworth Sleepiness Scale or apnea-hypopnea index were found at follow-up.

Paper 3 was a prospective study with the aim of evaluating the effect of tonsillectomy in adults with obstructive sleep apnea and tonsillar hypertrophy. We included 28 patients with an apnea-hypopnea index of >10 and large tonsils (Friedman tonsil size 3 and 4). The mean apnea-hypopnea index was reduced from 40 units/h to 7 units/h ($p<0.001$), while the mean Epworth Sleepiness Scale was reduced from 10.1 to 6.0 ($p<0.001$) at the six-month follow-up after surgery. Minor and moderate swallowing dysfunction was found in seven of eight patients investigated before surgery and the swallowing function improved in 5 of them after surgery, while no one deteriorated.

In Paper 4, we investigated the morphologhy and cytoarchitecture in 2 normal palate muscles, musculus uvula and musculus palatopharyngeus. Human limb muscles were used as reference. Muscle samples were taken post mortem from 5 previously healthy adult subjects, 2 infants and by biopsy procedure from 5 healthy non-snoring adult male subjects. The findings showed that the soft palate muscle fibers have a cytoskeletal architecture and cellmembrane complex that differs from that of the limb muscles. While all limb muscles showed immunoreaction for antibodies directed against different domains of cytoskeletal proteins desmin and dystrophin, a subpopulation of palate muscle fibers lacked or had a faint immunoreaction for desmin and the C-terminal of the dystrophin molecule. These proteins are otherwise considered ubiquitous and important for the integration and contraction of muscle cells. Our findings indicate an evolutionary specialization of the upper airway muscles, enabling them to perform intricate oropharyngeal functions.

Conclusions

No case of death related to surgery, in the form of uvulopalatopharyngoplasty, uvulopalatoplasty or nasal surgery for snoring or sleep apnea, has been recorded in Sweden among 4,876 patients treated between 1997 and 2005. Radiofrequency surgery of the soft palate has no effect on daytime sleepiness, snoring or apnea frequency in snoring men with mild or no sleep apnea and is therefore not recommended. Tonsillectomy is an effective treatment for obstructive sleep apnea in adults with large tonsils and is recommended as a first-line treatment for this group of patients. Furthermore, we show that a subgroup of muscle fibers in the human soft palate appears to have special biomechanical properties and their unique cytoarchitecture must be taken into account while assessing function and pathology in oropharyngeal muscles.

List of publications

This thesis is based on the following papers:

1. Frequency of serious complications after surgery for snoring and sleep apnea. Franklin KA, Haglund B, Axelsson S, Holmlund T, Rehnqvist N, Rosén M. Acta Otolaryngol. 2011 Mar;131(3):298-302.

2. Effects of radiofrequency versus sham surgery of the soft palate on daytime sleepiness. Holmlund T, Levring-Jäghagen E, Franklin KA, Lindkvist M, Berggren D. Laryngoscope. 2014 Oct;124(10):2422-6.

3. Tonsillectomy for obstructive sleep apnea in adults with tonsillar hypertrophy. Holmlund T, Franklin KA, Levring Jäghagen E, Lindkvist M, Larsson T, Sahlin C, Berggren D. Laryngoscope. Accepted for publication.

4. Unique expression of cytoskeletal proteins in human soft palate muscles. Shah F, Berggren D, Holmlund T, Levring Jäghagen E, Stål P. J Anat. 2015 Nov 24.

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Definitions

AASM American academy of sleep medicine
AHI The mean number of apneas and hypopneas per hour of sleep
AROUSAL A change in EEG pattern without awakening
BMI Body mass index
BNSQ Basic Nordic sleep questionnaire
CPAP Continuous positive airway pressure
ECG Electrocardiogram
EDS Excessive daytime sleepiness
EEG Electroencephalogram
ESS Epworth Sleepiness Scale
FOSQ Functional outcomes of sleep questionnaire
HYPOPNE A 50% reduction in airflow compared with baseline, in combination with an oxygen desaturation of $\geq$3%
MSLT Multiple sleep latency test
OA Oral appliance
ODI Oxygen desaturation index
OHS Obesity hypoventilation syndrome
OSA An obstructive apnea-hypopnea index of 5 or more
OSAS An obstructive apnea-hypopnea index of 5 or more, in combination with symptoms such as excessive daytime sleepiness
PG Polygraphy
PSG Polysomnography
RCT Randomized clinical trial
RDI Respiratory disturbance index
SDB Sleep-disordered breathing
SF-36 Short form 36
UPP Uvulopalatoplasty
UPPP Uvulopalatopharyngoplasty

Sammanfattning på svenska

Snarkning och obstruktiv sömnapné (OSA) är idag en global folksjukdom. Snarkning är det ”oljud” som uppstår när luftvägen under sömn förminskas och vävnaden börjar vibrera under andning. Vid obstruktiv sömnapné faller vävnaden samman och blockerar luftflödet till lungorna. Ett andningsuppehåll, en s.k. *apné* inträffar. Ett andningsuppehåll kan pågå allt ifrån några sekunder till mer än en minut och kan uppstå hundratals gånger per natt. För att klassificeras som en patologisk apné enligt internationell standard måste andningsuppehållet vara längre än 10 sek.

Snarksjukdomen förvärras sannolikt över tid och övergår succesivt i obstruktiv sömnapné med ökande antal andningsuppehåll under sömn. Detta leder till ett stresspåslag för kroppen med oftast uttalad dagtrötthet och en mängd negativa hälsoeffekter. Snarksjukdom och sömnapné ökar risken för bl.a. högt blodtryck och hjärt-kärlsjukdom samt också för att den drabbade ska orsaka trafikolyckor på grund av försämrad koncentrationsförmåga och trötthet.

En del av den negativa utvecklingen från snarkning till sömnapné anses bero på att snarkvibrationer kan ge neuromuskulära skador i gom och svalg. Dessa vävnadsskador anses också vara orsaken till att personer som snarkat länge ofta uppvisar störd sväljningsfunktion i form av felsväljning, där maten i uttalade fall hamnar i luftstrupen istället för i matstrupen.

I dagsläget är förstahandsbehandling vid sömnapné CPAP, en mask som placeras över näsa och mun och som skapar ett övertryck i luftvägen vilket förhindrar att luftvägen faller samman och att andningsstopp uppstår. CPAP har enligt flera studier den bästa effekten mot andningsuppehåll. En annan vanlig behandling är en bettskena som för underkäken nedåt och framåt så att luftvägen bli mer öppen. Bettskenan är en vanlig och effektiv behandlingsmetod för personer utan kraftig övervikt vid vanemässig snarkning eller måttlig sömnapné.

För ett tjugotal år sedan var kirurgi förstahandsmetoden vid behandling av snarkning och måttlig sömnapné. Man utförde då ofta operationer i svalg och gomm, s.k. gomplastiker. Bruket av kirurgisk behandling har dock minskat med tiden, dels p.g.a. biverkningar men också för att det saknades vetenskapliga studier som bevisade att kirurgin gav önskad och långsiktig effekt. Kirurgi utgör dock fortfarande ett komplement till behandling av snarkning och sömnapné när CPAP eller bettskena av olika skäl inte fungerar eller kan tolereras av patienten.

Även barn kan lida av snarkning och sömnapné men behandlingsprinciperna för barn skiljer sig från dem hos vuxna och berörs inte i avhandlingen.

I denna avhandling studeras: i) biverkningsfrekvenser efter olika typer av snarkkirurgi, ii) effekten av radiovågsbehandling i mjuka gommen på vuxna män med snarkning, iii) effekten av att operera bort halsmandlarna på vuxna med sömnapné och stora halsmandlar, iv) muskelvävnadens struktur och molekylära uppbyggnad i mjuka gommen hos friska personer som inte snarkar.

Avhandlingen består av fyra delstudier:

1. En registerstudie med kartläggning av svåra biverkningar efter kirurgi i form av uvulopalatopharyngoplastik, uvulupalatoplastik samt näskirurgi för behandling av sömnapné och snarkning och utfört i Sverige mellan åren 1997-2005. Studien omfattade 4 876 patienter. Inga dödsfall noterades. Komplikationsrisken var störst vid operationer där man tog bort delar av mjuka gommen samt halsmandlarna, där i snitt 37 av 1000 opererade fick biverkningar, framförallt p.g.a. infektioner eller blödningar.

2. I en prospektiv, randomiserad placebostudie utvärderades effekten av radiovågsbehandling i mjuka gommen vid snarkning och lindrig sömnapne. Trettiotvå patienter lottades till att få radiovågsbehandling eller placebo behandling. Patienterna visste inte vilken grupp de tillhörde. Vid uppföljning efter 12 månader var det inga statistiska belägg för att radiovågsbehandling minskade vare sig antal andningsuppehåll eller dagtrötthet.

3. Effekten av att ta bort halsmandlarna på patienter med stora halsmandlar och olika grad av sömnapné utvärderades i denna studie. Totalt deltog 28 patienter. Vid uppföljning 6 månader efter operationen hade antalet andningsuppehåll sjunkit drastiskt, från i snitt 40 till 7 andningsuppehåll per timme nattsömn. Inga allvarliga biverkningar uppstod. Dessa fynd talar för att man som förstahandsmetod ska erbjuda patienter med sömnapné och stora halsmandlar att ta bort halsmandlarna.

4. I detta projekt undersökte vi utseendet och uppbyggnaden av cellskelettet i två normala muskler i mjuka gommen hos friska personer utan känd snarkning och sömnapné. Muskler från armar och ben användes som referens. Fynden i studien visar att de normala muskelfibrernas uppbyggnad i mjuka gomen skiljer sig från jämförade muskler i armar och ben. Detta kan vara ett uttryck för en evolutionär utveckling för att möjligöra de komplexa funktioner som krävs av svalgets muskulatur.

Sammanfattningsvis kan vi konstatera: *Att* inga dödsfall har skett i Sverige efter operationer i gom, svalg eller näsa, utförda för att behandla snarkning och sömnapné under åren 1997 till 2005. *Att* radiovågsbehandling av mjuka gommen hos snarkande män med lindrig sömnapné inte har någon effekt på dagtrötthet, snarkning eller andningsuppehåll vid uppföljning efter 12 månader. Metoden kan därför inte rekommenderas. *Att* när man opererar bort stora halsmandlar på personer med andningsuppehåll så leder detta ofta till att andningsuppehållen minskar drastiskt. Metoden kan därför oftast rekommenderas som en förstahandsbehandling för denna patientgrupp. *Att* mjuka gommens muskelfibrer är uppbyggda på ett unikt sätt indikerar att deras specifika biomekaniska egenskaper skiljer sig från referens muskler i armar och ben.

Introduction/Background

Habitual snoring occurs in 11-15% of women and 20-28% of men[1-3], increasing up to the age of around 60 years.[4,5] Snoring is associated with a number of negative health effects, including daytime sleepiness, hypertension, cardiovascular disease and the impairment of cognitive functions.[6-8]

Obstructive sleep apnea is characterized by recurrent episodes of partial or complete upper airway obstruction during sleep.[9] It is a common disorder with a mean of 22% (ranging from 9% to 37%) in men and 17% (ranging from 4% to 50%) in women, according to 11 epidemiological studies of different cohorts, published between 1993 and 2013.[10]

It has been suggested that snoring can progress to obstructive sleep apnea due to the trauma, which the vibrations inflict in the pharyngeal tissues during snoring. This might cause loss of neuromuscular function diminishing the ability to keep the airway patency.[11] However, deeper investigations are required to establish this link.

Studies have shown that adults may have obstructive sleep apnea due to hypertrophy of the lymphoid tissue in the upper airway.[12,13] A previous study from our research group has shown that, among patients seeking a medical cure due to snoring, both men and women with large tonsils have an independent risk factor associated with an apnea-hypopnea index (AHI) of > 15. We found that 6% of 801 participants in this survey, including both men and women, had large tonsils.[14]

Obstructive sleep apnea is a risk factor for cardiovascular diseases, e.g. hypertension and stroke, diabetes, gastroesophagal reflux, impaired swallowing function and traffic accidents.[15]

Today, continuous positive airway pressure (CPAP) and oral appliances (OA) are commonly used as an effective treatment for sleep apnea. These methods are associated with a low incidence of serious adverse effects.[16,17] However, not all patients are able to comply with or adapt to these methods and a wide range of surgical techniques is therefore also available. Some of these can, however, lead to severe side effects.

Radiofrequency surgery of the soft palate was introduced by Powel et al. (1998) with the aim of reducing snoring and mild sleep apnea.[18,19] The method became popular because of its simplicity as an outpatient procedure with a low risk of adverse postoperative effects.

Uvulopalatopharyngoplasty (UPPP), with the removal of the tonsils and parts of the soft palate, has been used worldwide for decades to treat snoring and sleep apnea.[20] However, a known and persistent side-effect that sometimes occurs after UPPP is swallowing disorder.[21]
Tonsillectomy, in which the palate and uvula remain intact, has not shown the more severe side effects of UPPP and is today a routine method for recurrent infections and tonsillar hypertrophy in children.[22] Only a few studies of tonsillectomy alone as surgical treatment for obstructive sleep apnea in adults have been published and the cohorts are small.[23-26] Further, there are few prospective, randomized, controlled studies of the outcome of the surgical treatment of snoring and obstructive sleep apnea. The overall aim of the present PhD thesis is therefore to investigate the effects and side effects of common surgical methods, including UPPP, radiofrequency surgery of the soft palate and tonsillectomy. Furthermore, the structural and molecular build up of upper airway neuromuscular components in normal subjects will be analyzed. The findings of this study will form the basis for our future projects to examine the effect of snoring and sleep apnea on upper airway tissue and how it contributes to the pathophysiology of sleep disorderdered breathing. The overall outcome of our projects will hopefully benefit patients in form of more efficient treatment strategies in the future.

Clinical characteristics of snoring and obstructive sleep apnea

Snoring prevalence

Snoring is common and self-reported habitual snoring is found in one in seven women and one in four men.[1-3] The cause of the sound is usually described as a partial obstruction in the airway and subsequent vibrations in the oro- and hypopharynx. Snoring is associated with a number of negative health effects, including daytime sleepiness, hypertension, cardiovascular disease and the impairment of cognitive functions.[27-29] The prevalence increases up to the years immediately before retirement.[30,31] Snoring is more common among men than women, but the difference between the genders tends to decrease with age. Snoring increases daytime sleepiness even in the absence of OSA. The relative risk of having hypertension is elevated among habitual snorers.[32] Lindberg et al. (1998) reported an elevated risk of overall mortality and cardiovascular mortality specifically among men with habitual snoring and excessive daytime sleepiness.[30] Snoring is known to elevate the risk of atherosclerosis in the carotid arteries and this risk increases with the degree of snoring.[33] To date, there is no golden standard for the objective measurement of snoring and any evaluation of snoring is therefore reliant on subjective reports from patients and their bed partners.

OSA prevalence

Young and colleagues in the USA performed one of the most cited studies regarding the prevalence of OSA at the beginning of the 1990s. It showed a prevalence of 2% in women and 4% in men. The same study reported that obstructive sleep apnea is a common disorder, with a prevalence of 24% among men and 9% among women in a population of middle-aged adults, 30-60 years of age.[34] These numbers still apply globally, but it is reasonable to speculate that, with increasing weight gain in most of the world's populations the numbers will rise.[35] A follow-up study 20 years after Young's study showed a prevalence of OSA among 6% of women and 14% of men, in which 58% of the cases were caused by overweight.[36] A recent study of the prevalence of sleep-disordered breathing in the general population of Lausanne, Switzerland, showed that 23% of the women and 50% of the men among 3,043 investigated persons, median age of 57, had some degree of OSA.[37]

A review article by Franklin et al. (2015) presented data from 11 epidemiological studies from between 1993 and 2013 that showed a prevalence of OSA in a mean of 22% (range, 9-37%) of men and 17% (range, 4-50%) of women.[10] They also presented the finding that OSA prevalence increases with age and weight and is more prevalent in men than women.[10]
Snoring, apneas and hyponeas is caused by obstruction in the airway. The airway collapses, partially or totally during sleep, when there is reduced muscle tension. When the lumen of the airway is reduced, the Bernoulli effect causes further collapsibility in reducing the lateral wall pressure.
The obstruction, partial or total, causes elevated suction pressure in the thorax when the patient breathes. This suction power can cause acid reflux from the ventricle and also cause arousals. These arousals are associated with an elevated sympathetic activation, even during daytime, with raised levels of catecholamines, which in turn affects blood pressure and the risk of cardiovascular disease. The change in breathing pattern causes a disturbed level between the partial pressure of blood oxygen and carbon dioxide, further elevating the risk of morbidity.[38]

Traffic

OSA covaries with traffic accidents.[15] Young and coworkers described a three- to seven-fold increase in the risk of traffic accidents among men with snoring or OSA and an AHI of > 5 .[39] Hortsman et al. compared 156 patients with an AHI of >10 with healthy controls and found a four times higher risk of traffic accidents compared with controls.[40] If a person is suffering from sleep apnea or other illnesses with sleep disturbance, it is illegal according to Swedish law for them to drive and the Swedish transport administration can withdraw the driver's license unless the person is proven to have been treated successfully.[41]

OSA symptoms

Snoring and a history of apneas and daytime sleepiness are the most common symptoms. However, nycturia, dry mouth when waking up from sleep, pain from the throat, heartburn/reflux, recurrent awakenings, poor sleep quality, headaches, irritability, depression, impotence and many other symptoms are also common in OSA. These symptoms can have a substantial impact on the quality of life of the affected individuals.

Negative health effects

There is a close relationship between OSA and stroke and the converse also applies. In a meta-analysis from 2010, comprising 29 articles and 2,343 patients, Johnson et al. showed that sleep-disordered breathing with an AHI of > 5 occurred in 72% of patients with a previous stroke or transient ischemic attack patients.[42] Yaggi et al. (2005), followed 1,022 patients for a median of 3.4 years and reported a doubling in the risk of stroke or death with an AHI of > 5, regardless of confounders and treatment for sleep apnea at baseline.[43]

Hypertension according to the WHO is defined as arterial blood pressure of more than 140/90 mmHg in otherwise healthy subjects. In 2000, Peppard et al. followed 709 subjects in the Wisconsin cohort sleep study for four years. They found that, in a dose-dependent relationship, sleep apnea was an independent confounder related to hypertension. The odds ratio (2.89) almost tripled for having hypertension for patients with an apnea-hypopnea index of 15 or above compared with non-apneic subjects.[44] In a study by Bratton et al., CPAP treatment had no effect on blood pressure in patients with minimal symptomatic OSA.[45] There is an association between OSA and coronary artery disease, which also complies with OSA and diabetes mellitus.[10]

Furthermore, there is a relationship between mortality and OSA. Both the Winsconsin Study and the Sleep Heart Health Study, described a correlation with a higher mortality rate among patients with increasing numbers of apneas.[46,47]

Snoring-induced damage and neuropathy of the upper airway

Snoring causes vibrations in the tissue of the upper airway. Over time, these vibrations can cause tissue damage. In 1991, Woodson et al. described peripheral nerve degeneration in biopsies from the uvula and soft palate in snorers.[48] In 2001, Svanborg et al. proposed that vibrations from snoring can cause local neuromuscular trauma.[49] In 1998, Friberg described reduced vasodilatation after electrical stimulation in the oropharynx of OSAS patients, proposing an afferent nerve lesion.[11] This leads to impaired motor and sensory nerve functions. Sunnergren et al. showed a correlation between the degree of sensory neuropathy, described as cold detection thresholds in the soft palate, and the severity of the obstructive sleep apnea disorder.[50]

The function of swallowing is intricate and complex; both the efferent (V, VII, XII) and afferent (IV, IV, X) functions are innervated by different cranial nerves. These functions are affected among snorers and patients with OSA.[51] In addition to swallowing difficulties and a higher risk of aspiration, these nerve lesions also lead to the increased collapsibility of the upper airway.[49,52] There are also signs of changes in muscles as increase in fiber size variabillity, abnormal mitochondrial distribution and a low capillary supply in the upper airway tissue as a result of the vibration trauma that snoring and OSA cause.[48,53-55]

Impaired swallowing function

A person with obstructive sleep apnea can experience obstructive swallowing difficulties due to tonsillar hypertrophy. However snoring vibrations might cause neuropathic disturbances in the tissue of the oropharynx, resulting in the disturbed coordination of the oropharyngeal swallowing phase with a risk of aspiration.[56,57] After surgery with partial resection of the soft palate, persistent swallowing dysfunction with a risk of aspiration is often observed as a side effect.[58] One hypothesis is that the complication appears because the patient reaches a limit when parts of the tissue, including the nerve endings, which are important for eliciting the swallowing reflex, are removed and the patient is no longer able to compensate for the loss in sensibility.

When surgery only includes the tonsils, while the areas important for eliciting the swallowing reflex are not affected, it can lead to improvements in the obstructive swallowing problems. To our knowledge, there are no reports of long-term swallowing difficulties after tonsillectomy alone.

Diagnostic methods

Questionnaires

ESS

The Epworth Sleepiness Scale was published by Johns in 1991 as a time-saving and less expensive method than the MSLT for differentiating people with excessive daytime sleepiness from alert individuals.[59] The ESS consists of eight questions from situations with little activity in daily life, each with a four-point scale. The score ranges from 0-24 and, the higher the score, the higher the level of daytime sleepiness. The ESS has been proven to correlate to the AHI in the Sleep Heart Health Study, showing higher levels on the ESS when the AHI was higher.[60] There is also a correlation between the incidence of road traffic accidents and the ESS, as well as health-related questions relating to quality of life and the ESS. There are, however, contradictory results, with no correlation to the AHI, as presented by Chervin and Aldrich in 1999 and Osman et al. in 1999.[61,62]
Although the ESS is frequently used as a measurement tool for assessing OSA, since it is easy and inexpensive to perform, concerns have been raised about its reliability and validity. As mentioned in the beginning, the ESS has been validated against the MSLT, but the MSLT and ESS are not 100% equal. The MSLT is one of the instruments used for diagnosing narcolepsy, to measure and quantify sleepiness in those patients. The MSLT measures sleepiness at the time of the test, while the ESS measures sleepiness in the near past. These differences have also been described and, in 1999, Chervin and Aldrich showed no correlation between the two methods and these findings were also reported by Barbe et al. in 2001.[61,63] It has been shown that the intraindividual differences in the test can be somewhat high. Ngyuen and colleagues conducted a retrospective study in which 142 patients were evaluated and they were able to show that 23% of the patients answered differently in the sequential ESS score by five scale points or more.[61]

Setting these topics aside, the ESS is still one of the most used questionnaires in the field of OSA.

The Epworth Sleepiness Scale

The Epworth Sleepiness Scale is widely used in the field of sleep medicine as a subjective measure of a patient's sleepiness. The test is a list of eight situations in which you rate your tendency to become sleepy on a scale of 0, no chance of dozing, to 3, high chance of dozing. When you finish the test, add up the values of your responses. Your total score is based on a scale of 0 to 24. The scale estimates whether you are experiencing excessive sleepiness that possibly requires medical attention.

How Sleepy Are You?
How likely are you to doze off or fall asleep in the following situations? You should rate your chances of dozing off, not just feeling tired. Even if you have not done some of these things recently try to determine how they would have affected you. For each situation, decide whether or not you would have:

- No chance of dozing =0
- Slight chance of dozing =1
- Moderate chance of dozing =2
- High chance of dozing =3

Write down the number corresponding to your choice in the right hand column. Total your score below.

Situation	Chance of Dozing
Sitting and reading	•
Watching TV	•
Sitting inactive in a public place (e.g., a theater or a meeting)	•
As a passenger in a car for an hour without a break	•
Lying down to rest in the afternoon when circumstances permit	•
Sitting and talking to someone	•
Sitting quietly after a lunch without alcohol	•
In a car, while stopped for a few minutes in traffic	•

Total Score = ____________________

Analyze Your Score

Interpretation:

0-7: It is unlikely that you are abnormally sleepy.
8-9: You have an average amount of daytime sleepiness.
10-15: You may be excessively sleepy depending on the situation. You may want to consider seeking medical attention.
16-24: You are excessively sleepy and should consider seeking medical attention.

Reference: Johns MW. A new method for measuring daytime sleepiness: The Epworth Sleepiness Scale. *Sleep* 1991; 14(6):540-5.

SF-36

The Short Form-36 is a questionnaire that evaluates the quality of life in eight different health-related domains. It has been translated to Swedish and has also been evaluated.[65]

The Basic Nordic Sleep Questionnaire

This questionnaire was developed in the Nordic countries with the aim of developing a standardized questionnaire. The taskforce developing it was set up in 1988 by the Scandinavian Sleep Research Society. It consists of 21 questions on sleep, evaluating the past three months. The questions can be answered on a five-point scale, 1 to 5.[66]

FOSQ

The Functional Outcomes of Sleep Questionnaire is a self-reported measurement designed to assess the impact of disorders of excessive sleepiness on multiple activities of everyday living.[67]

OSA diagnosis

History

Historically, snoring has frequently been described in the literature since long ago. Between 1836-1837, Charles Dickens wrote *The Pickwick Papers* in which he describes an obese boy by the name of Joe who has symptoms similar to today's obesity hypoventilation syndrome. The Pickwickian syndrome was, however, first described in 1956 by Bickelmann et al.[68] In 1983 Lugaresi et al. wrote the theory of "The heavy snorer's disease", describing a progression from snoring to sleep apnea.[69] Guilleminault and colleagues described a syndrome called UARS or upper airway resistant syndrome where snoring patients had arousals that could be detected when there were no apneas present.[70] The term "sleep hypopnea syndrome" was presented by Gould et al. in 1988 and is now part of the apnea-hypopnea index.[71] The threshold for OSA was suggested by Guilleminault et al. in 1978 and was set at an apnea index of 5 or more with a minimum length of 10 seconds for the apnea.[72] These rules still apply today.

The golden diagnostic method is polysomnography, which, besides measuring airflow, respiratory movements of the chest and abdomen, oxygen saturation, heart rate and body position, also measures the level of sleep by EEG. A simpler method and one that is also less labor/resource demanding is ambulatory polygraphy, which lacks the EEG and therefore makes it more difficult to evaluate the actual sleep time, while the arousals cannot be measured.[15]

According to the American Academy of Sleep Medicine, the following criteria should be used to give a diagnosis of obstructive sleep apnea syndrome.[73]

Diagnostic criteria for OSA

A person must fulfill criterion A or B, as well as criterion C.

A. Excessive daytime sleepiness that is not better explained by other factors.

B. Two or more of the following that are not better explained by other factors:
– choking or gasping during sleep
– recurrent awakenings from sleep
– unrefreshing sleep
– daytime fatigue
– impaired concentration.

C. Overnight monitoring demonstrating five or more obstructive breathing events an hour during sleep. These events may include any combination of obstructive apneas/hypopnoeas or respiratory effort-related arousals.

OSA scoring

Obstructive apnea/hypopnea event

A transient reduction or complete cessation of breathing. In routine clinical practice, it is not considered necessary to distinguish obstructive hypopneas from apneas, while they are both included in the apnea-hypopnea index. The events must fulfill criterion 1 or 2, plus criterion 3, of the following.

1. A clear decrease (greater than 50%) from baseline in the amplitude of a valid measurement of breathing during sleep. Baseline is defined as the mean amplitude of stable breathing and oxygenation in the two minutes preceding the onset of the event, or the mean amplitude of the three largest breaths in the two minutes preceding the onset of the event (in individuals without a stable breathing pattern).

2. A clear amplitude reduction of a validated measurement of breathing during sleep that does not meet the above criterion but is associated with either oxygen desaturation of > 3% or an arousal.

3. The event lasts 10 seconds or longer.

Mixed and central apneas

In central apneas, there is also a cessation of airflow but no effort to breathe is made. Central apneas are more common among people with ischemic heart disease and then as Cheyne-Stokes respiration with a breathing pattern that increases and decreases, followed by a central apnea. When a mixed apnea occurs, it is a combination of both obstructive and central, usually starting with reduced central respiratory drive and followed thereafter by an obstruction.

An apnea was defined as a cessation of airflow lasting at least 10 seconds, while a hypopnea was defined as a 50% reduction in airflow compared with baseline, in combination with an oxygen desaturation of ≥3%.

Polygraphy

Overnight ambulatory sleep apnea recordings include continuous recordings of airflow using nasal cannula pressure, thoracic and abdominal respiratory effort, finger pulsoximetry and a body position sensor. Compared with polysomnography, polygraphy does not measure EEG. The disadvantage of this is that sleep time is estimated and there is therefore a risk that the actual sleeping time is scored as longer than it actually is, reducing the measured apnea-hypopnea index compared with the real value. Another disadvantage of this is that arousals cannot be detected. The Swedish Council of Technology Assessment in Health Care describes a high sensitivity (0.93) and specificity (0.92) when recordings are scored by a human and include measurements of respiratory movements, oxygen saturation levels and nasal airflow.[15] All the sleep recordings in this thesis have been performed manually using this method. (Fig.1 and 2)

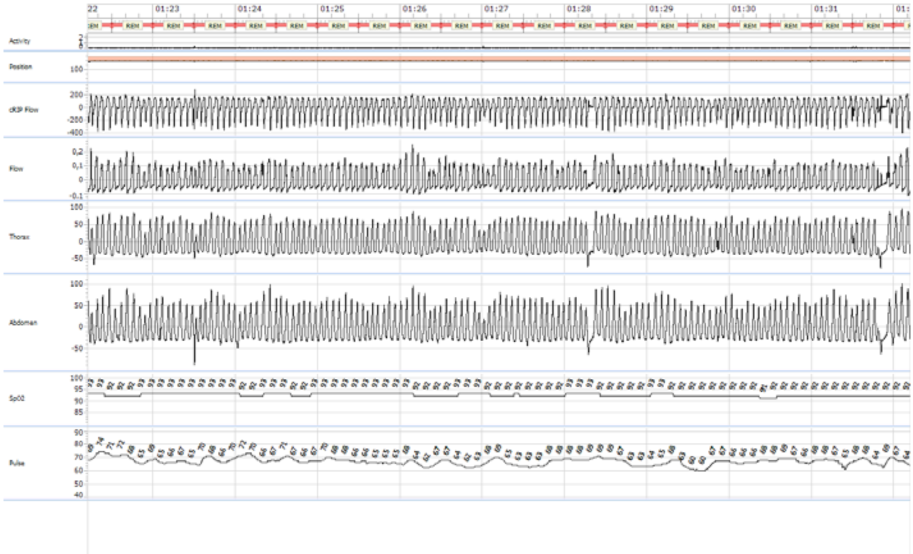

Fig.1 A normal polygraph

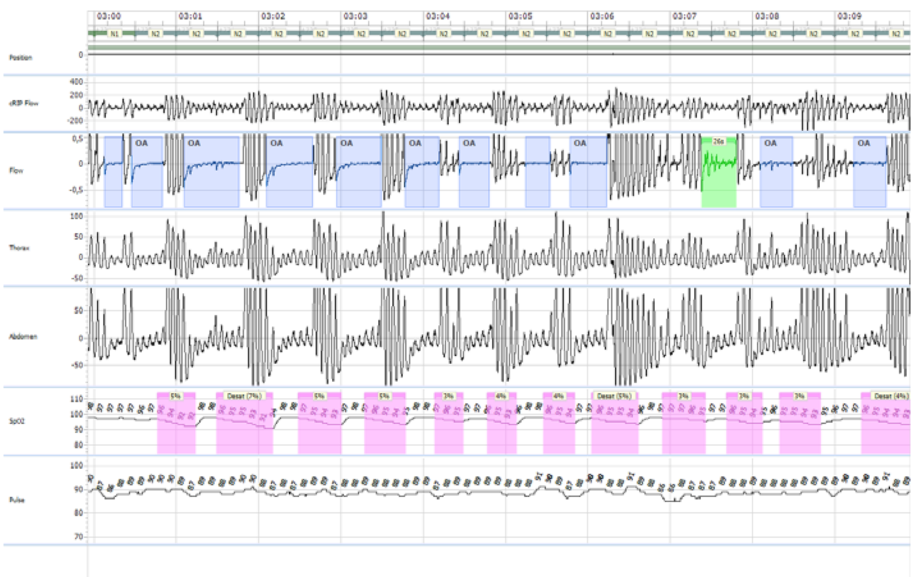

Fig.2 A polygraph from a patient with obstructive sleep apnea

OSA treatment

Non-surgical

Weight reduction

Fat distribution is important and changes in AHI are best predicted by changes in abdominal fat and airway length.[74] There is evidence that patients with a small maxillomandibular skeletal size may benefit most from weight loss. Studies have shown that OSA in itself may be obesogenic, with anabolic hormone deficiency (GH, testosterone), leptin resistance and increased ghrelin, which promotes a positive energy balance and is also associated with a lack of motivation to exercise.[74] The greater the OSA severity, the closer the correlation to smaller reductions in body and visceral fat and also smaller improvements in glucose metabolism when OSA patients lose weight.[75] Even CPAP treatment has been shown to be a obesogenic factor, increasing weight among users, as shown in the APPLE study by Quan in J Clin Sleep Med in 2013.[76] Finally, it is important to remember that not all obesity leads to OSA, not all weight loss will cure OSA and that OSA also occurs in non-obese persons.

CPAP

CPAP is the golden standard of treatment for OSA. It was presented by Sullivan and coworkers at the beginning of the 1980s and soon became popular because of its efficacy.[77] It is a machine that delivers continuous positive airway pressure via an electric fan. The positive pressure delivered via the machine creates a supporting opening force for the airway, preventing a collapse and following hyponeas and apneas. Since its introduction in 1981, its use has become the most common and effective treatment for OSA.

The Cochrane Collaboration and the Swedish Council on Technology Assessment in Health Care (SBU) have both presented evidence that CPAP reduces daytime sleepiness and treats obstructions in the airway.[78,15] The technical advances of the machine have made it easier to use and therefore have increased adherence. There are current auto-titrating CPAPs which are self-adjusting in terms of airway pressure and are also usually fitted with a heater and vaporizer.[78]

Like other treatments for OSA, CPAP has known side effects: nasal congestion, nasal dripping, skin irritation, eye irritation and mouth dryness.

All these side effects are connected to the use of CPAP and will vanish if the use is interrupted.

Oral appliances

Oral appliances (OAs) or mandibular advancement devices are devices that are usually custom made for the patient and fitted correctly by a dentist. These appliances are designed to push the mandible forward and slightly downwards in order to create a more open airway.

OAs have become the second most used treatment for OSA, after its introduction by Soll et al. in 1985.[79] An OA is usually less effective than CPAP when it comes to lowering the AHI, but it is often used more frequently and, in many studies, it is preferred when compared with CPAP. Cochrane's review of oral appliances says: *"CPAP appears to be more effective in improving sleep disordered breathing than OA. The difference in symptomatic response between these two treatments is not significant"*.[80] A study by Phillips et al. from 2013 found that OA was superior to CPAP in terms of improving quality of life and not inferior to CPAP in terms of impact on subjective sleepiness, 24-hour blood pressure, aortic stiffness and driving-simulator performance.[81]

Some side effects have been reported and they are mainly due to changes in occlusion. They can take the form of jaw and tooth pain, hypersalivation, muscle stiffness and dry mouth.[82]

Surgery

History

Tracheostomy was the first described surgical treatment for OSA and it is still in use, albeit rarely and with obvious side effects. In 1964, Ikematsu presented his surgical method for the treatment of habitual snorers. The method described a partial reduction of the soft palate and uvula.[83] The method was modified by Fujita in 1981, who then described the uvulopalatopharyngoplasty (UPPP), which also includes a tonsillectomy.[84] During the 1980s and 1990s, the UPPP became popular, but concerns were raised about the method and adverse effects were reported.[85,86] Since then, the method has been modified to be less radical and more tissue saving. Today, surgery is seldom the first line of treatment for OSA. Instead, it often works as a supplement or a means of enabling other types of treatment.

Tonsillectomy

Tonsillectomy is common all over the world. In Sweden, in 2014, 7,241 tonsillectomies were performed, making it one of the most performed surgical modalities.[22]

The first known report of tonsillectomy was made by Celsus. It dates back to 10 AD, in his *De medicina*, chapter vii, sect. 12, where he writes: *"Tonsils which remain indurated after inflammation, if covered by a thin membrane, should be loosened by working the finger round them and then torn out; but, when this is not practicable, they should be seized by a hook and excised with a scalpel"*.

Today, the indication for tonsillectomy is usually recurrent infections and obstruction. It is the first line of treatment for children with symptoms of obstructive sleep apnea if tonsillotomies are also included. Apart from pain, postoperative hemmorhage is the most common side-effect and, in 2014 in Sweden, around 7% of the patients were readmitted because of bleeding.[22]

Tracheostomy

A tracheostomy bypasses the obstruction in the upper airway and several studies have shown that it is a 100% effective method for reducing obstructive apneas.[87,88] The method used to be one of few surgical methods for treating OSA, but it is seldom used today.

Uvuluopalatopharyngoplasty

Uvulopalatopharyngoplasty, with the removal of the tonsils and parts of the soft palate, has been used worldwide for decades to treat snoring and sleep apnea.[84] A recent well-performed RCT by Browald et al. reported high efficacy when using this surgical method to reduce the apnea-hypopnea index in patients with obstructive sleep apnea.[20] However, 30-40% of the treated patients suffer from persistent swallowing dysfunction after surgery affecting the soft palate.[15,21,91,92] A recent study from our group reported a peri- and postoperative complication rate of 3.71% among patients who underwent UPPP in Sweden between 1997 and 2005, mainly because of bleeding and infections.[93] In 2004, Kezirian et al. reported serious postoperative complications at a rate of 1.5% among 3,130 patients at the veterans' affairs hospitals in the United States.[86] The same study reported a mortality rate of 0.2%. The Swedish study from our group found no mortalities after UPPP.[93]
In UPP surgery is restricted to the soft palate and uvula.

Radiofrequency surgery of the soft palate

Radiofrequency surgery of the soft palate was introduced by Powel et al. in 1998 with the aim of reducing snoring and mild sleep apnea.[18] The method became popular because of its simplicity as an outpatient procedure with a low risk of adverse postoperative effects.[19] The technique uses temperatures from 85° to 100°C that are delivered to the soft palate by a wand causing controlled scarring, designed to shrink and stiffen the tissue in the applied area. The long-term effects and efficacy of this treatment have been questioned.[94-96]

Weight loss by surgery

Obesity is the main risk factor for OSA. Weight loss, both as a weight reduction by dieting and via bariatric surgery, is effective in lowering the BMI, AHI and daytime sleepiness measured using the ESS, where bariatric surgery has been proven more effective.[97] Even though both methods work, the great challenge is to maintain the lowered weight.

Upper airway stimulation

Stimulation to the medial portion of the hypoglossal nerve activates protrusors of the tongue. A small electrode is installed and connected to a pacemaker, which the patient activates when going to sleep. The pacemaker then activates the pharyngeal muscles, maintaining an open airway. Van De Heyning et al. concluded that upper airway stimulation in patients with moderate to severe sleep apnea and CPAP failure was safe and efficacious and an improvement in the AHI, ESS and FOSQ could be seen at the six-month follow-up.[98] A study by Strollo from 2014, NEJM, showed that two-thirds of the patients responded to the therapy, reducing their AHI and ESS and increasing their FOSQ values.[99] This type of surgery/treatment is still under development.

Maxillomandibular advancement

Maxillomandibular advancement is a surgical technique in which the naso-, oro- and hypopharyngeal space is widened. The surgical correction of the bones in the upper airway is performed by moving the maxilla anteriorly, using a Le Forte 1 osteotomy, and in the mandible, using a sagittal split osteotomy. A recent meta-analysis by Zaghi et al. included 45 studies with a total of 518 patients and showed a significant reduction in the AHI and RDI in 512 of 518 patients (98.8%).

The ESS scores and the postoperative desaturation rate were also significantly reduced. The meta-analysis showed a surgical cure (AHI<5) rate of 38.5% among patients with AHI data and 19.1% among patients with RDI data.[100] This type of surgery is fairly invasive and the complication rate has been shown to comprise 1% of major complications and 3.1% of minor complications.[101]

Other surgical methods

There is a wide range of other types of surgery on different levels of the upper airway. Nasal surgery, such as septal plasty and conchotomy, can aid breathing, reduce snoring and improve adherence to other types of therapy, such as CPAP. The soft palate can be injected with sclerosing agents and different types of palatal implant have been investigated, with the aim of stiffening the soft palate. Different types of surgery on the tongue have been presented, with a reduction in the size of the tongue base and the body of the tongue, as well as repositioning surgery to prevent the tongue from falling posteriorly, obstructing the airway.[102,103] Other levels that have been performed is hyoid suspension.[104]

Aims

The overall aim of the present PhD thesis is to investigate the effects and side effects of common surgical methods, including UPPP, radiofrequency surgery of the soft palate and tonsillectomy. Furthermore, morphology and cytoarchitecture of upper airway muscles in normal subjects will be investigated.

Paper 1: A retrospective database study investigating the frequency of serious complications, including death, after surgery for the treatment of snoring and sleep apnea.

Paper 2: A randomized, placebo controlled study evaluating the effect on daytime sleepiness after radiofrequency surgery of the soft palate in snoring men with mild or no sleep apnea.

Paper 3: A prospective study evaluating the effect of tonsillectomy on sleep apnea in adults with obstructive sleep apnea (OSA) and tonsillar hypertrophy.

Paper 4: A histological study investigating the morphologhy and cytoarchitecture of muscle fibers in human soft palate muscles with immunohistochemical and morphological techniques. This study forms the basis for ongoing and future investigations of the effects of snoring and sleep apnea on these muscles.

Materials and methods

Subjects and methods

Paper 1

A total of 4,876 patients, aged 25 and older, who had been discharged from in-hospital care, or out-patient treatment, all with a primary diagnosis of sleep apnea or snoring (ICD-10 codes G47.3 and R06.5 respectively) and surgically treated from 1 January 1997 to 31 December 2005, were identified in the National Patient Register at the Center for Epidemiology at the Swedish National Board of Health and Welfare. This register has had full coverage of in-patient care in Sweden since 1987 and an increasing amount of out-patient surgery since 1997. All surgical procedures are classified according to the NOMESCO Classification of Surgical Procedures (NCSP). Every Swedish citizen has a unique 10-digit identification number. A personal identification number was obtained from the National Patient Register for all patients of interest. This identification number was then linked to the National Cause of Death Register in order to obtain peri- and postoperative mortality within 30 days of surgery. (Table I)

Table I. Mean age and comorbidity per 1000 patients

Status	Number	Age (years)	Cancer	Cardiovascular disease	Respiration disease	Obesity
No surgery	31 140	54.1	35	196	102	50
Surgery	4876	45.8	19	96	140	7
Total	36 016	53.0	34	187	109	44

Data are standardized for age for the whole population in 10-years classes

Surgical procedures

Uvulopalatopharyngoplasty (UPPP) was defined as the removal of the tonsils, the uvula and parts of the soft palate and a pharyngeal plasty, according to NCSP codes ENC40 (uvulopalatopharyngoplasty) or ENC30 (pharyngeal surgery) in combination with EMB10 (tonsillectomy). Uvulopalatoplasty (UPP), with the removal of the uvula and parts of the soft palate using a laser (LAUP) or a scalpel, was defined as NCSP code ENC30.

(Fig.3) Nasal surgery was equated with NCSP codes DHB40 (conchotomy), DHB50 (conchoplasty) or DJD20 (nasal septal surgery).

Complications and re-operations were obtained from the National Patient Register, while mortality within 30 days of surgery was obtained from the National Cause of Death Register. Severe complications following surgery were reported when complications according to the ICD-10 codes of T81 or T88.2-T88.9 were recorded at the time of surgery or at re-admission within 30 days of surgery. Peri- and postoperative mortality were obtained within 30 days of surgery. Re-operation for snoring and sleep apnea was identified up to 365 days after surgery.

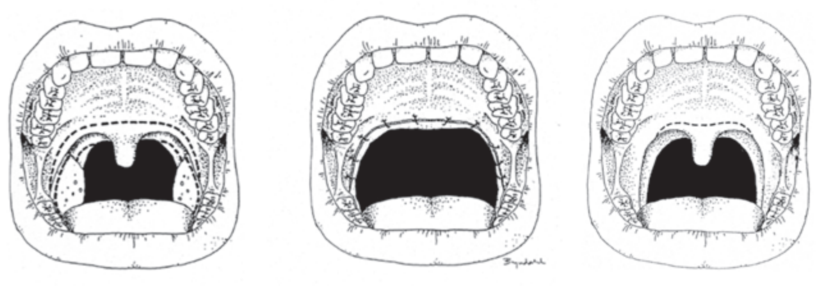

Fig. 3 Schematic drawing illustrating the surgical technique of UPPP and UPP. Dotted lines indicate the mucosal incisions.

Paper 2

Thirty-five men were recruited from consecutive patients referred to the Ear, Nose and Throat Clinic due to snoring and complaints of daytime sleepiness. The inclusion criteria were male gender, age 18 to 65 years, an apnea-hypopnea index (AHI) of ≤ 15 and a body mass index (BMI) of ≤ 31. The exclusion criteria were smoking, prior palatal surgery, or severe systemic disease (American Society of Anesthesiologists class ≥ 3). The eligible group comprised 68 consecutive patients referred to the Ear, Nose and Throat Clinic. Eighteen patients declined participation and 15 patients were excluded due to smoking or cardiovascular disease. (Table II)

Table II.

Baseline patient demographics and clinical characteristics

	Surgery (n=20) Mean (SD)	Sham surgery (n=15) Mean (SD)	p[1]
Age	47.6 (7.5)	49.9 (7.9)	0.404
Weight	85.0 (9.8)	84.4 (9.1)	0.866
BMI	26.5 (2.2)	26.2 (1.7)	0.608
ESS	9.8 (3.5)	10.0 (5.0)	0.918
AHI	4.6 (3.6)	4.6 (2.6)	0.983
Self-rated health	n (%)	n (%)	
Excellent	4 (20)	1 (7)	
Very good	7 (35)	8 (53)	
Good	7 (35)	4 (27)	
Fairly good	2 (10)	2 (13)	
Poor	0 (0)	0 (0)	

[1] Independent samples t-test ESS = Epworth Sleepiness Scale score, AHI = Apnea Hypopnea Index self-rated health: questions drawn from the SF-36 questionnaire

Randomization

The participants were randomly assigned to either radiofrequency or sham surgery by means of prefilled closed envelopes. Initially, there were 50 envelopes containing 25 radiofrequency surgery notes and 25 sham surgery notes. Reception personnel, who were not involved in the study or surgical procedure, randomly selected one envelope and wrote the patient's name and date of birth on it before it was handed over to the surgeon, who was sitting in a separate room. The surgeon opened the envelope and the patient was given treatment according to the note in the randomly distributed envelope. The patients were blinded to their treatment alternative. Twenty patients were randomized to surgery of the soft palate and 15 to sham surgery.

Questionnaires

The primary outcome was daytime sleepiness using the ESS measured at follow-up, one year after treatment. The ESS is a questionnaire on the probability of falling asleep in different situations in daily life.[59] The secondary outcomes were the AHI and subjective snoring according to a bedroom partner, with questions relating to the frequency and level of snoring. All patients participated in an overnight sleep apnea recording. The Basic Nordic Sleep Questionnaire (BNSQ), with five possible answers to each question, was used to evaluate "snoring frequency", "snoring intensity", "daytime sleepiness" and "the probability of falling asleep at work".[66] According to questions drawn from the Short Form-36 Health Survey questionnaire regarding general health, the participants evaluated their health level to be on a par with that found for the general population in Sweden.[65]

Sleep recordings (Studies 2,3,4)

Overnight ambulatory sleep apnea recordings (Embletta, Embla systems, Kanata, Canada) included continuous recordings of airflow using nasal cannula pressure, thoracic and abdominal respiratory effort Xact Trace Belts (Embla Systems, Kanata, Canada), finger pulsoximetry (Nonin Oximeter XPOD, Nonin Medical, Inc., Plymouth, USA) and a body position sensor. All the recordings were scored manually and the duration of sleep was estimated from the recordings. The scorer was blinded to treatment and the scoring was not performed by any of the authors. An apnea was defined as a cessation of airflow lasting at least 10 seconds, while a hypopnea was defined as a 50% reduction in airflow compared with baseline, in combination with an oxygen desaturation of ≥ 3%.[9]

Radiofrequency and sham surgery

The radiofrequency and sham surgery procedures were performed in an out-patient setting. All patients were given a topical lidocaine spray, 10 mg/dose on the soft palate, followed by an injection of approximately 4 ml of carbocain 1%. In the radiofrequency group, the Coblator surgery system 1 (Arthro-care Corp, Sunnyvale, CA) was used to administer high-frequency energy via the ReFlex Ultra 55 Plasma Wand to the soft palate. The machine settings were set at level 6. The wand was inserted into the muscular layer of the soft palate and held in place for 10 seconds at each of the three sites in the soft palate, in the midline 1 cm below the border of the hard and soft palate and 1 cm laterally on both sides, fig. 4.

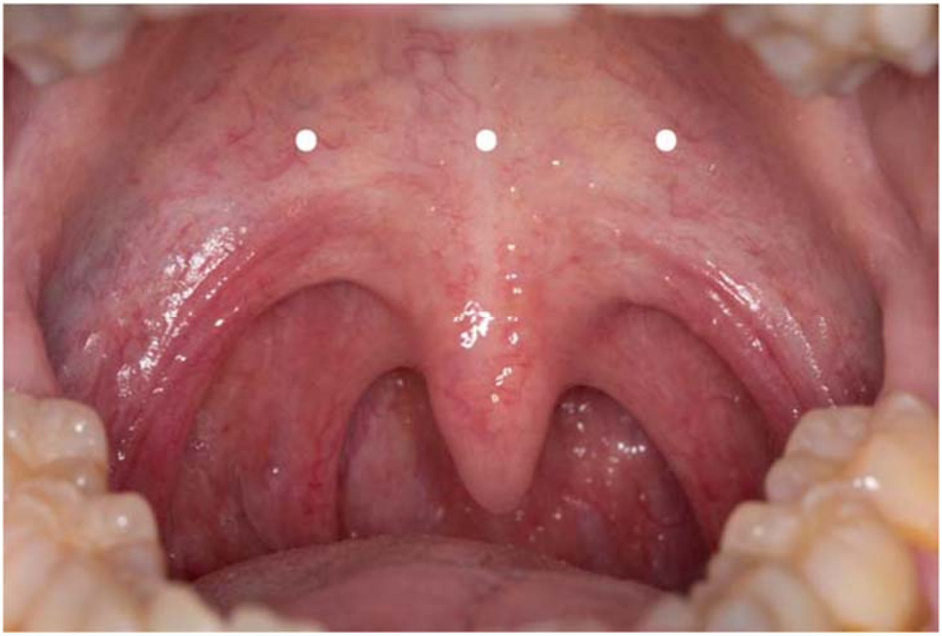

Fig. 4 The three treatment locations in the soft palate.

The same setting for local anesthesia, wand and machine was used in the sham surgery group, except that no energy was supplied to the wand. The patients were offered a non-steroidal anti-inflammatory drug as a postoperative painkiller. No antibiotics or corticosteroids were prescribed. The patients were given the option of receiving up to three treatments. All the patients chose to receive three treatments, with the exception of one patient in the radiofrequency group who chose only one treatment. The treatment sessions took place at four- to six-week intervals.

Changes in voice or swallowing function were evaluated with questionnaires at baseline and follow-up.

Paper 3

Twenty-eight participants were recruited from three ENT clinics in northern Sweden in 2011-2014 to undergo tonsillectomy. The inclusion criteria were men and women from 18 to 59 years (Fig. 5), AHI > 10 and concomitant tonsillar hypertrophy, size 3 and 4, according to Friedman's classification (Fig. 6-9).[105] The exclusion criteria were smoking, previous palatal surgery, severe systemic disease (ASA class ≥ 3) and BMI > 32. All patients with obstructive sleep apnea symptoms and concurrent large tonsils were possible candidates for inclusion in this trial. After a clinical examination with an assessment of tonsil size according to Friedman's classification, patients underwent ambulatory polygraphic sleep registration and BMI control. Eight patients included at the centre in Umeå underwent a fluoroscopic swallowing examination and questions regarding dysphagia were answered before and six months after surgery as a subgroup. All patients were informed of a non-surgical treatment such as CPAP. If severe obstructive sleep apnea was diagnosed, the patient was supplied with a fitted CPAP prior to surgery to be used during his/her immediate postoperative period as a risk reduction.

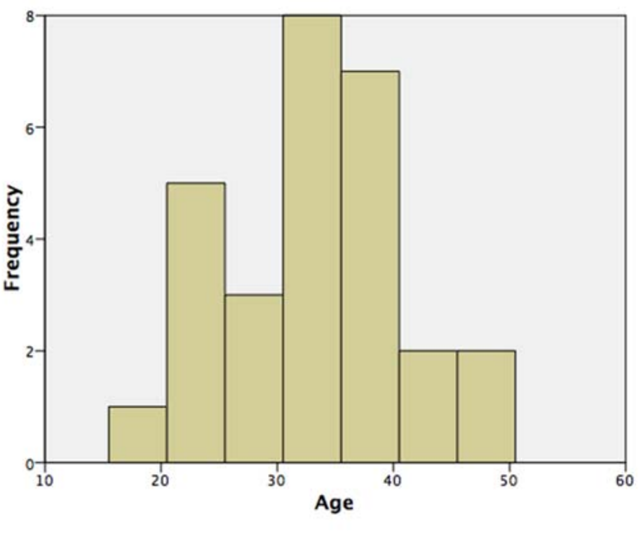

Fig. 5 Age distribution

Fig. 6 Tonsil size 1, are hidden within the pillars

Fig. 7 Tonsil size 2, extend to the pillars

Fig. 8 Tonsil size 3, extend beyond the pillars but not to the midline

Fig. 9 Tonsil size 4, extend to the midline

All pictures from Otolaryngol Head Neck Surg 2002;127:13-21

Questionnaires

The secondary outcome was daytime sleepiness using the ESS.[59] The questionnaires were answered at the time of and six months after surgery. Questions regarding pharyngeal disturbance and snoring were also answered prior to the radiographic examination.

Videofluoroscopy (Studies 3,4)

The videoradiographic examinations of oral and pharyngeal swallowing function were performed in lateral and frontal projections. The patient swallowed a liquid contrast bolus (barium sulfate) and chewed and swallowed a solid standard bolus (crispbread (Falu Rågrut) with barium sulfate contrast). The patient was placed in an upright position comfortable for swallowing. The examinations were stored and interpreted at full speed and slow motion. The examination of swallowing function was performed with the C-arm, Philips BV 29, field width 23 cm, grading of swallowing: 1. Normal function, 2. Mild dysfunction; in the presence of either: repeated premature leakage, velar dysfunction, residual, or laryngeal penetration, 3. Moderate dysfunction: repeated deviant features in grade (2) or dysfunction of the upper esophageal sphincter, the epiglottis or the propagation wave, 4. Severe dysfunction: aspiration and 5. Inability to swallow. All examinations were stored on Super-VHS videotape (Panasonic Super VHS VCR) and reviewed by two of the authors.

Radical tonsillectomy

The extracapsular tonsillectomy was performed under general anesthesia and with oral intubation. The procedure was performed using either a cold steel or radiofrequency technique using the Coblation system® (Arthrocare Corp, Sunnyvale, CA). The patients were observed over night at a postoperative care unit. The surgery was performed by different ear, nose and throat surgeons, at the three participating centers. The patients were observed over night and the majority used CPAP treatment as an extra security measure.

Paper 4

Healthy adult male samples

Muscle samples were collected by biopsy procedure from 5 healthy adult male subjects (mean age 40 years, range 31-51 years). These samples were acquired under local anesthesia with carbocain at the base of the uvula and in the anterior-superior region of the palatopharyngeal arch. All biopsies were obtained from non-snoring subjects with normal oropharyngeal function, evaluated with a videofluoroscopic examination of swallowing function. The absence of sleep-disordered breathing was confirmed by overnight sleep registration (Somnologica PSG software, Embla, Broomfield, CO, USA).

Post-mortem samples

Autopsies from the uvula and the palatopharyngeus muscle were collected post mortem from five previously healthy adult subjects (two males, three females, mean age 54 years, age range 46-75 years).

All ten subjects but one had a normal body constitution according to body mass index (< 30 kg m^2). None of them was receiving medical treatment and there was no history of any significant disease, alcohol or drug abuse. In addition, autopsy samples were taken from two male infants (age 4 months and 1.4 years). For comparison, muscle samples from six healthy voluntary adult subjects were taken from a thigh muscle, musculus vastus lateralis, and an arm muscle, musculus biceps brachii. These two limb muscles are known to have a mixed population of fibers expressing myosin heavy chain (MyHC)I or MyHCII. Their morphology, muscle fiber type composition and cytoskeletal build-up are well studied and established.

Immunohistochemistry

The muscle samples were mounted for transverse sectioning in OCT compound (Tissue Tek, Miles, Elkhart, IN, USA), rapidly frozen in liquid propane chilled with liquid nitrogen and stored at -80°C until further processing. Some samples were fixed before freezing using 4% formaldehyde in 0.1 M phosphate buffer, pH 7.0, for 24 h at 4°C. The samples were then washed overnight at 4°C in Tyrodes solution containing 10% sucrose. Serial muscle cross-sections, 5 μm thick, were cut in a cryostat at -20°C and mounted on glass slides. Immunohistochemical staining was performed using modified standard techniques and well-characterized monoclonal and polyclonal antibodies.

Questionnaires

Questions regarding daytime sleepiness were answered using the Epworth Sleepiness Scale (ESS).[59] Questions regarding pharyngeal disturbance and snoring were also answered prior to the radiographic examination.

Ethics

All the patients in all studies gave their informed written consent to participate. The regional ethical review board in Umeå approved studies 2,3 and 4. Study 1 is register based and no individual results were presented, so ethical approval was not applicable.

Statistics

Paper 1: The data were presented as the number per 1,000 patients or as means and standard deviations. An adjusted odds ratio (95% confidence interval) was used for comparisons of different surgical procedures using logistic regression analysis with adjustments for gender, age and type of hospital.

Paper 2: The data were analyzed using PASW statistics version 20 (IBM, Armonk, NY). The descriptive results are presented as deviations, numbers and percentages. The normality assumptions for the quantitative variables were checked with histograms and skewness. When it came to quantitative variables, linear regression was used to estimate adjusted differences between groups adjusting for baseline values. The Mann-Whitney U test was used to investigate differences in ordinal variables between groups. The follow-up time is presented as the mean (Table IV). Statistical significance was defined as $P < 0.05$.

Paper 3: Descriptive statistics were presented with the mean and standard deviation. Measurements of the AHI and ESS were presented with the mean and confidence intervals. The normality assumption for the distribution of the change in the AHI and ESS were investigated with skewness. The distribution for the change in the AHI was at the limit for fulfilling the normality assumption, while the distribution for the change in the AHI satisfied the normality assumption. The change in the AHI and ESS was investigated with both a paired samples t-test and Wilcoxon's test.

Paper 4:
Descriptive study – no statistical evaluations

Results

Paper 1

A total of 4,876 patients were treated surgically. Uvulopalatopharyngoplasty was performed on 3,572 patients, uvulopalatoplasty on 929 patients and nasal surgery on 375 patients. None of the surgically treated patients died in the peri- and postoperative period. Severe complications, mainly bleedings and infections, were recorded in 37.1 per 1,000 patients treated with uvulopalatopharyngoplasty, in 5.6 per 1,000 patients after uvulopalatoplasty and in 8.8 per 1,000 patients after nasal surgery. (Table III)

Table III. Severe complications within 30 days from surgery

Surgery	No. of patients	No. of complications	Estimated no. of complications Per 100 patients	Adjusted odds ratio (95% confidence interval)*
UPP/LAUP	929	5	5.6	1
Nasal surgery	375	3	8.8	1.6 (0.4-6.6)
UPPP	3572	135	37.1	6.9 (2.8-16.9)
Total	4876	143	29.3	

*Estimated with logistic regression and adjusted for age, gender, and type of hospital

Paper 2

Thirty-two of 35 patients, 19 of 20 patients in the radiofrequency surgery group and 13 of 15 patients in the sham surgery group, completed the study. No differences between the two groups in relation to the ESS or AHI were found at follow-up. (Table IV). Radiofrequency surgery of the soft palate had no effect on daytime sleepiness, snoring, or apnea frequency in snoring men with mild or no sleep apnea one year after surgery.

Table IV.

Values at baseline and follow-up for the ESS and AHI

	Radiofrequency surgery (n=19) mean(SD)		Placebo (n=13) mean (SD)		Adjusted difference* (95% CI) at follow-up
	Baseline	Follow-up	Baseline	Follow-up	
ESS	9.84 (3.6)	8.05 (4.2)	10.23 (5.3)	8.31 (5.1)	0.10 (-1.87 to 2.07)
AHI	4.15 (3.1)	5.91 (4.8)	4.65 (2.8)	5.95 (4.8)	0.20 (-3.29 to 3.69)

*Function score adjusted for baseline and BMI (baseline).

Paper 3

Twenty-eight of 29 included patients were examined six months after surgery. One patient was lost to follow-up. The mean apnea-hypopnea index was reduced from a mean of 40 units/h (95% CI 28 to 51) to seven units/h (95% CI 3 to 10), $p < 0.001$, at the six-month follow-up after surgery (Fig. 10 and 11).

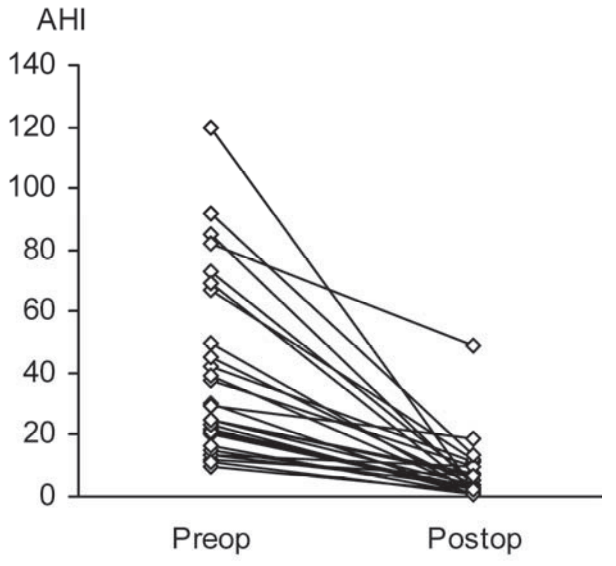

Fig. 10. AHI before and after tonsillectomy.

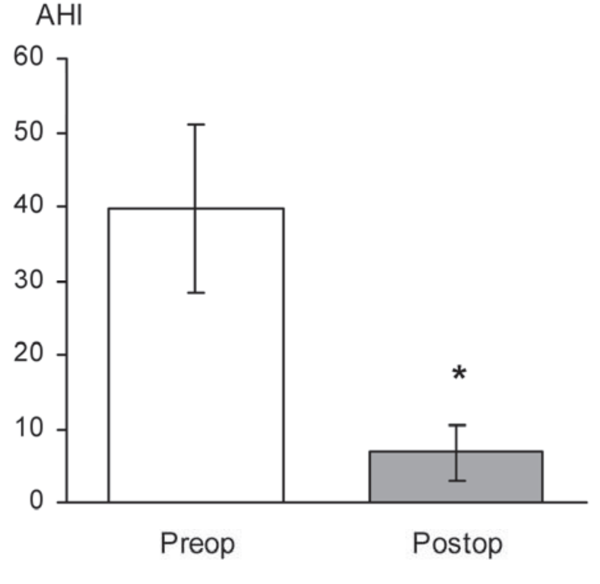

*Fig. 11. Apnea-hypopnea index before and after tonsillectomy. Bars indicate the mean and 95% confidence interval. *p <0.001.*

Before surgery, 13 patients (46%) had severe sleep apnea, eight patients (29%) had moderate sleep apnea and seven patients (25%) had mild sleep apnea. After tonsillectomy, one patient (4%) had severe sleep apnea, one patient (4%) had moderate sleep apnea, eight patients (29%) had mild sleep apnea and 18 patients (64%) no longer had sleep apnea (Fig. 12).

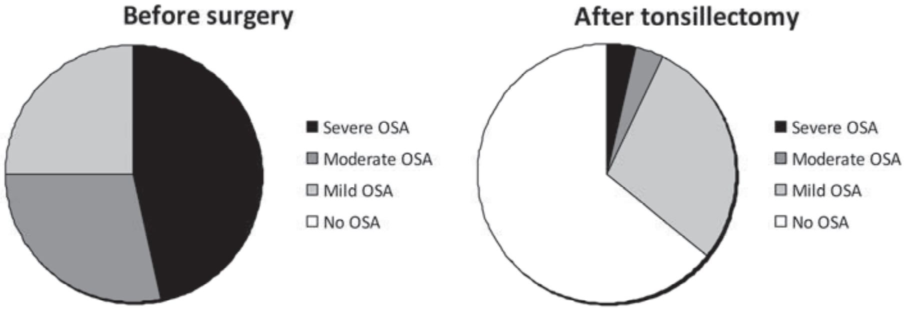

Fig. 12. Distribution of the severity of sleep apnea before and after tonsillectomy.

The apnea-hypopnea index was reduced from 36 (95% CI 22 to 51) to 5 (95% CI 3 to 7) ($p<0.001$) in patients with tonsil size 3 and from 47 (95% CI 27 to 68) to 11 (95% CI -1 to 23) ($p=0.002$) in patients with tonsil size 4. There was no difference in effect with regard to tonsil size 3 and 4, $p=0.628$.

Daytime sleepiness measured using the Epworth Sleepiness Scale was reduced from a mean of 11 (95% CI 8 to 13) to 6 (95% CI 4 to 7), $p < 0.001$, (Fig. 13) at the six-month follow-up after surgery.

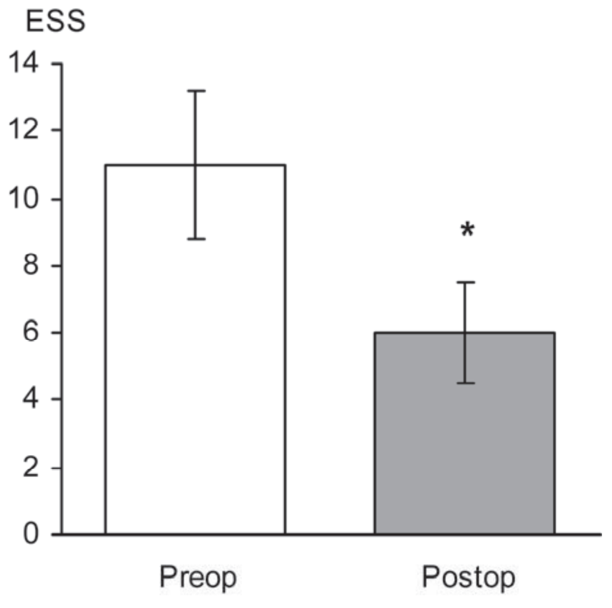

*Fig. 13 Epworth Sleepiness Scale (ESS) before and after tonsillectomy. Bars indicate the mean and 95% confidence interval. *p <0.001.*

Seven of 8 patients had a mild to moderate swallowing dysfunction before surgery. None of the patients experienced deterioration in swallowing function after surgery; five had an improved swallowing function at the postoperative examination. One patient had postoperative bleeding, which was treated with electro-cautery, and readmission over night and another patient reported numbness of the tongue lasting three weeks after surgery.

The findings show that the soft palatal muscle fibers have a cytoskeletal architecture that differs from that of the limb muscles. While all limb muscles showed immunoreaction to a panel of antibodies directed against different domains of cytoskeletal proteins, desmin and dystrophin, a subpopulation of palatal muscle fibers lacked or had a faint immunoreaction to desmin (UV 11.7% and PP 9.8%) and the C-terminal of the dystrophin molecule (UV 4.2% and PP 6.4%). The vast majority of these fibers expressed slow contractile protein myosin heavy chain I. Furthermore, an unusual staining pattern was observed in these fibers for β-dystroglycan, caveolin-3 and neuronal nitric oxide synthase (nNOS), which are all membrane-linking proteins associated with the dystrophin C-terminus. While the immunoreaction for nNOS was generally weak or absent, b-dystroglycan and caveolin-3 showed a stronger immunostaining.(Table V) The absence or a low expression of cytoskeletal proteins, otherwise considered ubiquitous and important for the integration and contraction of muscle cells, indicate a unique cytoarchitecture designed to meet the intricate demands of the upper airway muscles.

Table V. Immunostaining of the different antibodies in adult human soft palate and limb muscles. Positive immunoreaction in fibers/fiber membranes is marked (+) and absent staining is marked (-)

Antibody	Product Code	Palate muscles	Limb muscles
Dystrophin	GTX15277	-/+	+
Dystrophin	NCL-DYS1	+	+
Dystrophin	NCL-DYS2	-/+	+
Dystrophin	NCL-DYS3	+	+
Desmin	M0760	-/+	+
Desmin	18-0016	-/+	+
Desmin	ab15200	-/+	+
Laminin	PC 128	+	+
βeta-Dystroglycan	NCL-b-DG	-/+	+
Caveolin 3	610421	-/+	+
Neuronal nitricoxide synthase	AB5380	-/+	+
Vinculin	V9131	+	+
H-Nestin	MAB1259	-	-
Utrophin	sc-33700	-	-
α-Actinin	ab9465	+	+
Vimentin	sc-6260	-	-

Discussion

Sleep apnea and snoring are common and affect most of the population in conjuction with aging and weight gain. The need for different effective and manageable treatment modalities is therefore vast and important.

In our first study, we found that serious complications were most common after uvulopalatopharyngoplasty compared with other, less extensive surgical modalities. The study material was large and taken from two nationwide cohorts, the National Patient Register and the Swedish Cause of Death Register, which have full coverage of all patients regarding in-patient care and mortality. One positive finding compared with earlier studies was that no deaths were reported. This finding is probably due to more strict inclusion criteria for this type of surgery and awareness of complications. The SBU report that was published in Scandinavia in 2007 called for more high-quality studies, preferably RCTs, in the field of OSA surgery and this report has probably also contributed to knowledge and safer surgery.[15] One limitation in our study was that we were unable to explore the frequency of more long-term complications such as swallowing difficulties, which are well known and previously reported.

The second study in this thesis was an RCT, comparing radiofrequency surgery of the soft palate with placebo treatment in thirty-five men with snoring and mild sleep apnea. Here we found no effect, since there was no significant change in the AHI or ESS index compared with baseline at the 12-month follow-up. There were no major complications among the studied patients and the treatment was well tolerated. Earlier similar studies have shown an effect on reducing snoring with this technique but only in a relatively short time frame after the surgery was performed.[106] Our initial plan was to include this type of treatment at our department, but, due to the results, the procedure is no longer in use at our hospital.

Our third study was a prospective study, investigating the effect of tonsillectomy among patients with large tonsils and OSA. We found highly significant results, in terms of a reduction in both the AHI and ESS index after surgery compared with baseline. The initial plan was to design this study as an RCT, using half the included patients as a control group with a six-month delay to surgery compared with the other arm where the patients would undergo surgery immediately after diagnosis. This design was, however, turned down by the regional ethical review board in Umeå. It was considered unethical to let patients wait for treatment, since the preliminary results we reported were promising and the risk factors for OSA are severe.

As a subgroup, we examined the swallowing function among all patients included in Umeå. Here we found no deterioration after surgery; on the contrary there were improvements and less dysfunction after surgery. In a recent and well-performed randomized, controlled study of uvulopalatoplasty, the SKUP3 trial, by Browaldh et al. in 2104, high efficacy for uvulopalatoplasty in reducing the AHI in patients with OSA is shown.[20] However, some concerns have been raised about the clinical conclusions that can be drawn from the SKUP3 trial.[107] The patients in the trial were selected to exclude patients with previous tonsillectomy and Friedman stage III. The Friedman Stage I and II patients included in the SKUP3 trial had large tonsils by definition or, when the tonsils were small, the tongue was low. The surgery performed in the SKUP3 study was tonsillar resection, a limited palatal resection and suturing of the posterior tonsillar pillars. It is therefore difficult to know which part of the surgery contributed most to the reduction in the AHI. The 32 patients, men and women, in the intervention group of the SKUP3 had a mean age of 41.5 years at baseline, a mean body mass index of 28.2 and a mean AHI of 53.3. The corresponding figures in our present study are 28 patients, men and women, with a mean age of 33.4 years, a mean body mass index of 28.9 and a mean AHI of 39.8.[108] In the SKUP3 trial, the decrease in the AHI after the surgical intervention was 60%, a reduction from 53.3 to 21.1.[20] In our present study, the AHI was reduced by 83%, from preoperative values of 39.8 to 6.8 after tonsillectomy.[108] So, at least for OSA patients with tonsillar hypertrophy, i.e. tonsil size Friedman 3 and 4, it is unlikely that additional palatal surgery would be beneficial.

In the fourth study, we found that the muscles of the human soft palate differ from limb muscles in their expression of cytoskeletal proteins. The most interesting finding was a low or absent immune-response in a subgroup of muscle fibers for the Abs against the intermediate filament (IF) desmin and the C-terminal of dystrophin, while all fibers in limb muscles expressed a distinct immune-response for these Abs. In human muscles, abnormal expression or substitute isoforms of these ubiquitous cytoskeletal muscle proteins has only been reported in genetic disorders.

Force generation of the muscle sarcomeres is transmitted to sarcolemma and extracellular matrix by a complex network and interaction of cytoskeletal proteins. An important cytoskeletal protein required for this interaction is IF desmin. This protein is regarded to be ubiquitous in skeletal muscles. The atypical cytoskeletal architecture in a subpopulation of fibers in palate muscles, but not in limb muscles, provides further evidence that the fiber composition in cranial muscles are more complex than in limb muscles.[109] Another novel finding was the absence or low immunoreaction for the C-terminal domain of the dystrophin molecule in subpopulation palate muscle fibers. Interestingly, most of the fibers unreactive for antibodies against the dystrophin C-terminal were also unreactive for the Abs directed against other cell membrane molecules related to the dystrophin associated protein complex. This reflects that a subgroup of fibers may have special biomechanical properties in palate muscles i.e. influencing fiber stiffness, sarcolemmal deformability, stability of costameres, contraction velocity and transmission of forces to the extracellular matrix. The novel findings of an unique cytoarchitecture in a subgroup of normal soft palate muscle fibers most likely reflect specialization of the muscles to meet complex requirements in intricate oropharyngeal functions such as breathing, oral communication and swallowing. This must be taken into account while assessing pathology in oropharyngeal muscles affected by injury, such as vibratory/stretch damage in sleep-disordered breathing, or neuromuscular disorders.

We have ongoing studies in this field and, in the near future, we intend to present another paper which will determines if upper airway neuropathy (impaired sensory or motor nerve function) and/or myopathy (muscle weakness and wasting) correlate to the severity of snoring and obstructive sleep apnea and to disturbances in upper airway function. If we can establish that an acquired injury by snoring vibrations in the upper airways is a risk factor for pharyngeal dysfunction and OSA we will have substantial scientific evidence to implement new treatment strategies.

Conclusions

No case of death related to surgery, in the form of uvulopalatopharyngoplasty, uvulopalatoplasty or nasal surgery for snoring or sleep apnea, has been recorded in Sweden among 4,876 patients treated between 1997 and 2005.

Radiofrequency surgery of the soft palate has no effect on daytime sleepiness, snoring or apnea frequency in snoring men with mild or no sleep apnea and is therefore not recommended.

Tonsillectomy is an effective treatment for obstructive sleep apnea in adults with large tonsils and is recommended as a first-line treatment for this group of patients.

A subgroup of muscle fibers in the human soft palate appears to have special biomechanical properties and their unique cytoarchitecture must be taken into account while assessing function and pathology in oropharyngeal muscles.

Future perspectives

Airway obstruction is often caused by different anatomical variations and anatomy is probably the most common reason for development of OSA, even if recent studies have also identified non-anatomical explanations.

Owens et al. presented a model of physiological traits to predict OSA.[111] They described low pharyngeal muscle response during sleep, an overly sensitive ventilator control system (high loop gain) and, finally, a low respiratory arousal threshold as non-anatomical reasons for OSA. They also propose different types of treatment, such as drugs and training, to increase the muscle response in the upper airway. One example of a drug that improves upper airway tone is dronabinol, a synthetic form of a naturally occurring substance in the cannabis plant. It decreased daytime sleepiness and the apnea-hypopnea index by 30% in a pilot study of 22 patients.[112]

Certain sedatives, such as as trazodone[113], have been investigated as a means of raising the arousal threshold. Supplemental O_2 and CO_2 or drugs like acetazolamide have been trialed as a way of reducing the instability of the ventilator control.[112]

Zonisamide is another drug that has shown potential for both reducing apneic events and inducing weight loss among OSA patients in a study published by Eskandari et al. in 2014.[114] At four weeks, zonisamide reduced the apnoea-hypopnoea index by a mean ± sd of 33 ± 39% and the oxygen desaturation index by 28 ± 31%.

The ongoing global obesity epidemic has led to an increase in research to find new therapies in the battle aginst weight. In this field, there are numerous new experimental emerging drugs and it is to be hoped that they will provide for the effective and safe long-term treatment of obesity.[115]

Adults with a suspicion of OSA will probably be examined with a sleep registration, polygraphy or polysomnography. This is not the case when it comes to children. In children, it is usually the health history from the parents and the examination by the surgeon that determine whether or not they are going to be treated. This will probably change in the near future, since studies have shown that, even though surgery is performed, on tonsils and adenoids, one third still have residual OSA in a low-risk population and two thirds in a group of obese children, considered as high risk. This highlights the importance of follow-up and this applies to children as well.[111]

Finally, if our ongoing studies establish that snoring vibrations contribute to development of OSA, early intervention to stop snoring may have obvious beneficial effects in reducing the risk of future cardiovascular and other serious unhealthy events.

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