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**AIRWAY SURGERY FOR OBSTRUCTIVE  
SLEEP APNEA AND PARTIAL UPPER  
AIRWAY OBSTRUCTION  
DURING SLEEP**

by

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Perttu Halme

**Airway surgery for obstructive sleep apnea and partial upper airway obstruction during sleep.**

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**ABSTRACT**

This study analyzed the feasibility and efficacy of surgical therapies in patients with sleep-disordered breathing ranging from partial upper airway obstruction during sleep to severe obstructive sleep apnea syndrome. The surgical procedures evaluated were tracheostomy, laser-assisted uvulopalatoplasty (LUPP) and uvulopalatopharyngoplasty (UPPP) with laser or ultrasound scalpel.

Obstructive sleep apnea and partial upper airway obstruction during sleep were measured with the static charge-sensitive bed (SCSB) and pulse oximeter. The patients with severe obstructive sleep apnea syndrome were treated with tracheostomy. Palatal surgery was performed only if the upper airway narrowing occurred exclusively at the soft palate level in patients with partial upper airway obstruction during sleep. The ultrasound scalpel technique was compared to laser-assisted UPPP. The efficacy of LUPP to reduce partial upper airway obstruction during sleep was assessed and histology of uvulopalatal specimen was compared to body fat distributional parameters and sleep study findings.

Tracheostomy was effective therapy in severe obstructive sleep apnea. Partial upper airway obstruction and arterial oxyhemoglobin desaturation index during sleep decreased significantly after LUPP. The minimal retropalatal airway dimension increased and soft palate collapsibility decreased at the level where the velopharyngeal obstruction had occurred before the surgery. Ultrasound scalpel did not offer any significant benefits over the laser-assisted technique, except fewer postoperative haemorrhage events. The loose connective tissue as a manifestation of edema was the only histological finding showing correlation with partial upper airway obstruction parameters of SCSB.

Tracheostomy remains a life-saving therapy and also long-term option when adherence to CPAP fails in patients with obstructive sleep apnea syndrome. LUPP effectively reduces partial upper airway obstruction during sleep provided that obstruction at the other levels than the soft palate and uvula were preoperatively excluded. Technically the ultrasound scalpel or laser surgeries are equal. In patients with partial upper airway obstruction the loose connective tissue is more important than fat accumulation in the soft palate. This supports the hypothesis that edema is a primary trigger for aggravation of upper airway narrowing during sleep at the soft palate level and evolution towards partial or complete upper airway obstruction during sleep.

**Keywords:** sleep-disordered breathing, obstructive sleep apnea, partial upper airway obstruction during sleep, static charge-sensitive bed (SCSB), soft palate, laser-assisted uvulopalatoplasty (LUPP), histology, surgical efficacy.

Perttu Halme

**Hengitysteiden leikkaushoito obstruktiivisessa uniapneassa ja osittaisessa unenaikaisessa ylähengitystiehtaumassa.**

Korva-, nenä- ja kurkkutautioppi, Turun Yliopisto, Suomi.

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## TIIVISTELMÄ

Väitöskirjatyössä tutkittiin leikkaushoidon vaikuttavuutta obstruktiivisen uniapnean ja osittaisen unenaikaisen ylähengitystiehtauman hoidossa. Ensimmäisessä osatyössä selvitettiin hoitovaste silloin kun ahtaat ylähengitystiet ohitetaan kokonaan henkitorviavanteen kautta. Seuraavissa osatyöissä keskityttiin pehmeän suulaen leikkaushoitoihin, laser-avusteiseen uvulopalatoplastiaan (LUPP) ja uvulopalatopharyngoplastiaan (UPPP) joko laseria tai ultraääniveistä käyttäen.

Obstruktiivinen uniapnea ja osittainen unenaikainen ylähengitystiehtauma todennettiin unipatjarekisteröinnillä (static charge-sensitive bed, SCSB). Henkitorviavanteella hoidettiin vaikeaa obstruktiivista uniapneaoireyhtymää sairastavia potilaita. Pehmeän suulaen leikkaus tehtiin vain osittaista unenaikaista ylähengitystiehtaumaa sairastaville potilaille, joilla kliinisen tutkimuksen perusteella ylähengitystiehtauma sijaitsi pehmeän suulaen tasolla. UPPP:n teknistä suorittamista ja potilaan toipumista verrattiin kun toimenpide tehtiin joko ultraääniveitsellä tai laserilla. LUPP:n tehokkuus arvioitiin osittaisen unenaikaisen ylähengitystiehtauman hoidossa. Leikkauksessa poistetun pehmeän suulaen kudskoostumus analysoitiin ja löydökset suhteutettiin koko kehon rasvajakaumaan ja unirekisteröintilöydöksiin.

Henkitorviavanne hoiti tehokkaasti vaikean obstruktiivisen uniapnean. Lukuunottamatta hieman pienempää leikkauksen jälkeistä verenvuototaipumusta ultraääniveitsi ei tarjonnut oleellista hyötyä laseravusteiseen UPPP:n verrattaessa. Unenaikaisten hengityshäiriöiden kokonaismäärän merkitsevä väheneminen LUPP:n jälkeen selittyi osittaisen unenaikaisen ylähengitysahtauman vähenemisellä. Pehmeän suulaen ja nielun takaseinämän välinen etäisyys kasvoi ja pehmeän suulaen taipumus painua nielun takaseinää vasten väheni. Löysän sidekudoksen osuus pehmeässä suulaessa oli rasvakudoksen osuutta suurempi ja löysän sidekudoksen esiintyvyys korreloi osittaisen unenaikainen ylähengitystiehtauman esiintyvyyden kanssa.

Trakeostomia on tehokas hoitomenetelmä vaikeaa obstruktiivista uniapneaoireyhtymää sairastavilla potilailla, joilla on krooninen hengitysvajaus ja jotka eivät sopeudu CPAP-hoitoon. LUPP vähentää tehokkaasti osittaisen unenaikaisen ylähengitystiehtauman esiintymistä potilailla, joilla on ennen leikkausta poissuljettu muut ylähengitystiehtaumatason kuin pehmeän suulaen alue. Ultraääniveitsellä ja laserilla ei ole eroa UPPP:n teknisessä suorittamisessa eikä potilaan leikkauksen jälkeisessä seurannassa. Löysän sidekudoksen lisääntyminen on yksi mahdollinen mekanismi, jolla osittainen unenaikainen ylähengitystiehtauma voi edetä tai kehittyä obstruktiiviseksi uniapneaksi.

**Avainsanat:** obstruktiivinen uniapnea, osittainen unenaikainen ylähengitystiehtauma, unipatjarekisteröinti (static charge-sensitive bed, SCSB), pehmeä suulaki, laseravusteinen uvulopalatoplastia (LUPP), histologia, leikkaushoidon vaikuttavuus.

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**ABBREVIATIONS**

AHI	Apnea-hypopnea index
ASA	American society of anesthesiologists
BIA	Bioelectrical impedance analysis
BMI	Body mass index
CAPSO	Cautery-assisted palatal stiffening operation
CO <sub>2</sub>	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CT	Computed tomography
ESS	Epworth sleepiness scale
LAUP	Laser-assisted uvulopalatoplasty
LUPP	Laser uvulopalatoplasty, laser-assisted uvulopalatoplasty
LUPPP	Laser-assisted uvulopalatopharyngoplasty
MAA	Mandibular advancement appliances
MMA	Maxillo-mandibular advancement
MO	Mandibular osteotomy
MRI	Magnetic resonance imaging
NSAID	Non-steroidal anti-inflammatory drugs
ODI <sub>4</sub>	Arterial oxyhemoglobin desaturation index of 4%
OSA	Obstructive sleep apnea
OSAS	Obstructive sleep apnea syndrome
PSG	Polysomnography
RDI	Respiratory disturbance index
RFA	Radiofrequency ablation
SaO <sub>2</sub>	Arterial oxyhemoglobin saturation
SaO <sub>2</sub> <sup>mean</sup>	Mean arterial oxyhemoglobin saturation
SaO <sub>2</sub> <sup>min</sup>	Minimum arterial oxyhemoglobin saturation
SDB	Sleep-disordered breathing
TAP	Transpalatal advancement pharyngoplasty
UARS	Upper airway resistance syndrome
UPP	Uvulopalatoplasty
UPPP	Uvulopalatopharyngoplasty
VAS	Visual analogue scale
W/H-ratio	Waist/hip ratio
ZPP	Zetapalatopharyngoplasty

**Abbreviations related to the Static Charge-Sensitive Bed and breathing patterns**

ALL	Sum of various periodic breathing patterns and IRR
IRR	Increased respiratory resistance
OP-1	Obstructive periodic breathing type-1
OP-2	Obstructive periodic breathing type-2
OP-3	Obstructive periodic breathing type-3
P-1	Periodic breathing type-1
PLM, PMS	Periodic leg movements in sleep, periodic movements in sleep
SCSB	The static charge-sensitive bed
% of TIB	Percentage of time in bed

## **LIST OF ORIGINAL PUBLICATIONS**

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals I-IV.

- I Haapaniemi J, Laurikainen E, Halme P and Antila J. Long-term results of tracheostomy for severe obstructive sleep apnea syndrome. *ORL J Otorhinolaryngol Relat Spec.* 2001;63(3):131-6.
- II Halme P, Antila J, Antila H, Aho H, Polo O, Salminiitty H, Toskala E. Uvulopalatopharyngoplasty with an ultrasound scalpel or laser: is there a difference? *Eur Arch Otorhinolaryngol* 2010;267(4):635-42.
- III Halme P, Toskala E, Laurikainen E, Antila J, Tsushima Y and Polo O. LUPP relieves partial upper airway obstruction during sleep in patients with velopharyngeal narrowing. *Acta Otolaryngol* 2010;130(5):614-9.
- IV Halme P, Toskala E, Laurikainen E, Antila J, Jartti L, Tsushima Y, Kalimo H, Polo O. Body fat distribution and soft palate histology in patients with partial upper airway obstruction during sleep. Submitted.

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## 1. INTRODUCTION

Over the recent three decades, nasal continuous positive airway pressure (CPAP) has become the treatment of choice for patients with the obstructive sleep apnea syndrome (OSAS) (Polo et al. 1994). About two out of every three symptomatic OSAS patients adhere to CPAP and every third patient becomes noncompliant to CPAP over time (Meslier et al. 1998, McArdle et al. 1999, Grote et al. 2000, Anttalainen et al. 2007b). For these patients, other treatments, such as oral appliances or surgery, should be considered.

Permanent tracheostomy was introduced as the first curative treatment for OSAS, and it was used for the most severe forms of obstructive sleep apnea (OSA). Tracheostomy was replaced by uvulopalatopharyngoplasty (UPPP), by other surgical procedures and then by breathing assisting devices, like CPAP and oral appliances (Guilleminault et al. 1981). Currently, the mainstay of sleep apnea surgery is to use surgery to achieve less morbidity and a high cure rates.

The apnea-hypopnea based index may underestimate the significance of sleep-disordered breathing (SDB), especially early during the development of the condition. Therefore, evaluation of the treatment outcome needs to include more than only an assessment of obstructive or central apnea markers (Anttalainen et al. 2007a). The static charge-sensitive bed (SCSB) allows identification of not only episodes of apnea and hypopnea, but also of patterns specific for partial upper airway obstruction during sleep (Polo 1992). In this sense the SCSB method offers advantage over conventional polysomnography (PSG) for assessing treatment outcome. Patients with a low appearance of episodes of apnea but increased respiratory resistance during sleep, as in partial upper airway obstruction during sleep, may present with marked symptoms of daytime sleepiness or morning headaches, which respond to therapy. In patients with a mild OSAS, CPAP may result in a lower compliance rate in the long-term (Engleman et al. 1999). Many centres do not offer CPAP to patients with partial upper airway obstruction during sleep if there is low appearance of apneas. In the case of partial upper airway obstruction during sleep as the predominant form of SDB, surgery is one of the therapeutic options to relieve symptoms.

In an earlier study by Polo and colleagues severe obstructive apnea events were significantly reduced during sleep after UPPP in adult OSAS patients (Polo et al. 1989). Although obstructive apnea episodes decreased to one third, there was a significant increase of partial upper airway obstruction during sleep. Persistent SDB may contribute to recurrence of upper airway narrowing and apneas. Computer tomography (CT) showed no evidence of significant enlargement of the smallest cross-sectional area at the velopharyngeal level, i.e. in the area of the UPPP.

This study focused first on analyzing the overall effectiveness of surgery when all possible obstructive levels in upper airway were bypassed with tracheostomy. The idea was to assess the long-term success of tracheostomy for severe OSAS patients

by studying symptom questionnaires and SCSB findings. Patients with partial upper airway obstruction as the predominant breathing abnormality during sleep underwent uvulopalatal surgery due to a narrowed retropalatal airway. The study hypothesis was that in the patients with upper airway obstruction limited to the retropalatal airway, the surgical removal of excessive elongated tissues, with or without tonsil hypertrophy, improves SDB. The efficacy of uvulopalatal surgery was assessed by estimating the dimensions and collapsibility of the upper airway with digital fluoroscopy. The role of increased respiratory resistance during sleep and partial upper airway obstruction was also assessed as a factor possibly contributing to the secondary changes in the upper airway. Such changes may follow forced inspiratory efforts, creating increased intraluminal pressure during obstructive breathing. The histology of uvulopalatal tissue samples was compared with the findings at SCSB and with body fat distribution. Finally, the feasibility of new surgical instrumentation for uvulopalatal operation (ultrasound scalpel) was assessed.

## **2. REVIEW OF THE LITERATURE**

### **2.1. Sleep-disordered breathing**

SDB was first discovered as various forms sleep apnea. With improved monitoring techniques, also episodes of hypopnea were detected. Later, various forms of partial upper airway obstruction during sleep have been identified. Depending on the choice of the sensors, variable terminology has been used to describe these non-apneic phenomena.

The episodes of sleep apnea were originally classified as obstructive, central or mixed types (Jung and Kuhlo 1965). During OSA there is a cessation of airflow during the inspiratory phase despite continuing respiratory efforts until the subject is aroused and the patency of the upper airway is restored. After a few deep breaths the subject usually falls asleep again and breathing becomes obstructive again. The OSA events last usually 10 to 90 seconds and are repeated 30 to 90 times per hour of sleep. OSA is often associated with severe sleep fragmentation. OSA with excessive daytime sleepiness is called the OSAS.

Apnea and snoring are both reflections of the excessive narrowing of the upper airway during sleep (Kales et al. 1985). The prevalence of OSAS varies across different studies depending on the age and size of the study population, geographical factors, diagnostic methods and criteria. The prevalence of OSAS varies between 0.4 and 8.5% and is most common in the age group between 40 and 65 years (Telakivi et al. 1987). In the middle-aged population the prevalence of OSAS is assumed to be 4% among males and 2% among females (Gislason et al. 1988, Young et al. 1993, Kripke et al. 1997). Still, only a small fraction of this patient population is diagnosed and treated (Strollo and Rogers 1996). The finding that only a part of the affected population comes to the attention of physicians is corroborated by the results of Health 2000 survey in Finland which showed differences in the prevalence between OSAS diagnosed by physicians (2% male and 0.5% female) and a control population self reporting repetitive apneas during sleep (13% and 3%, respectively) (Aromaa and Koskinen 2002).

The role of partial upper airway obstruction during sleep has been studied since the early 1990's by Polo and colleagues. They have shown that partial upper airway obstruction during sleep is a common manifestation of SDB (Polo 1992). Recent studies have shown that the prevalence of SDB excluding snoring is even higher, if both obstructive periodic breathing and partial upper airway obstruction during sleep are taken into account (Polo-Kantola et al. 2003, Anttalainen et al. 2007a). Partial upper airway obstruction during sleep may also be detected with methods such as the SCSB or inspiratory flow shape analysis (Aittokallio et al. 2001).

Habitual snoring without apnea is the most common sleep-related breathing disorder. The prevalence of habitual snoring in the middle-aged female population is 5-15% and in the male 20-25% (Lugaresi et al. 1980, Koskenvuo et al. 1985). Snoring tends to increase with age (Knuiman et al. 2006): 30-40% of females and 50-60% of males are habitual snorers at age around 60 (Koskenvuo et al. 1985, McNicholas 2005).

Today the concept of SDB is understood to encompass two major categories. The first is related to sleep-induced muscle relaxation, predisposing a structurally narrow upper airway for collapse. During sleep this narrowed upper airway causes snoring, increased respiratory resistance or obstructive or mixed episodes of sleep apnea. The second factor is withdrawal of the wakefulness stimulus for breathing, which uncovers underlying abnormalities in the respiratory control system. Periodic breathing, Cheyne-Stokes respiration, central apnea and nocturnal hypoventilation are forms of SDB that arise from abnormal respiratory control during sleep. Often these two conditions overlap and interact. Their relative contributions to the SDB phenotype are affected by changes in body weight, concomitant cardiovascular diseases and increasing age. The symptoms related to SDB are presented in Table 1.

**Table 1.** Symptoms of SDB related to nighttime and daytime (Kales et al. 1985, American Academy of Sleep Medicine Task Force 1999, Bassiri and Guilleminault 2000).

<b>SYMPTOMS DURING NIGHT</b>	<b>SYMPTOMS DURING DAY</b>
Insomnia	Unrefreshing sleep
Snoring	Morning headaches
Restlessness	Fatigue
Awakenings	Falling asleep unintentionally
Choking / gasping	Excessive sleepiness
Witnessed apneas	Impaired concentration ability
Nocturia	Depression
Gastroesophageal reflux	Personality changes
Perspiration	Impaired sexual activity

## **2.2. Definitions**

### **2.2.1. Types of apnea and the apnea-hypopnea index**

Based on recordings on the airflow with oronasal thermistors and the respiratory drive with respiratory belts as part of the PSG, the episodes of sleep apnea are classified as obstructive, central or mixed ones. In an obstructive apnea episode, the upper airway is totally closed, usually at a level ranging from the velopharynx to the base of the tongue and the hyoid bone. The postural muscle tone decreases after the patient has fallen asleep. The respiratory activity of the upper airway muscles, which under wake conditions dilate the airway, is no longer sufficient to maintain the patency of the upper airway during sleep. During an episode of obstructive apnea, there is virtually complete



cessation of airflow; at most there is only 10% of the flow of the baseline amplitude which continues for a minimum duration of 10 seconds. In hypopnea airflow continues, but with a maximum amplitude of 30% of baseline, for a minimum duration of 10 seconds. Decreased airflow of hypopnea is associated with a parallel reduction of 4% or more in arterial oxyhemoglobin saturation ( $\text{SaO}_2$ ) (Iber et al. 2007). The severity of SDB is based on subjective symptoms and the apnea-hypopnea index (AHI), which is defined as the sum of all apnea and hypopnea episodes per hour of sleep (American Academy of Sleep Medicine Task Force 1999, Iber et al. 2007). It is also possible to present only apnea index, which is defined as the sum of all apnea episodes per hour of sleep. The respiratory disturbance index (RDI) includes AHI and also more subtle respiratory events such as the respiratory effort-related arousals (RERAs) which are characterized as arousal from sleep due to increased respiratory efforts. Decreased nasal pressure flow is also included under the definition of OSAS (American Academy of Sleep Medicine 2005, Iber et al. 2007).

If the patient is temporarily breathing more than the current state of the sleep requires, the cessation of respiratory efforts result in a central apnea. Central apnea should be considered as a physiologic response to episodic over-breathing, which is the same abnormality as associated with stroke or severe heart failure known as Cheyne-Stokes breathing (Naughton 1998). Episodes of central apnea can also result from over-breathing that occurs after arousals from prolonged episodes of OSA. Mixed apnea, which is a combination of central and obstructive apnea, may behave like obstructive apnea in terms of symptoms and therapeutic responses.

### **2.2.2. Partial upper airway obstruction**

In contrast to apnea and hypopnea, the concept of partial upper airway obstruction during sleep is more controversial. Depending on the recording technique, partial upper airway obstruction has been referred to various terminologies, which comprise subtle differences. Lugaresi (University of Bologna) called it obstructive hypoventilation or heavy snorer's disease (Lugaresi et al. 1975). Alihanka introduced the term increased respiratory resistance (IRR) to describe the gradually increasing respiratory efforts recorded by the SCSB (Alihanka 1987). In 1993, Guilleminault coined the term upper airway resistance syndrome (UARS), which he initially used to describe short episodes of increased esophageal pressure fluctuations ending in an arousal (Guilleminault et al. 1993). These episodes of UARS occurred often in lean women. The term UARS has evolved more or less into a synonym of IRR over time. Those, who consider that only the arousals and sleep fragmentation is important, use the term RERA. Those, who stress the importance of prolonged episodes of increased respiratory workload and increased intrathoracic pressure variation prefer the term IRR.

AHI encompasses only the episodes of apnea and hypopnea and defines SDB as it was done at the time when thermistors were used as airflow sensors. IRR without simultaneous

significant hypopnea or desaturation cannot be detected with thermistors. The severity of SDB will be underestimated, if it relies only on AHI (Polo 1992, Anttalainen 2008). It has been shown that even in patients with an AHI score of less than 5/hour (/h) IRR or periodic breathing without apnea may be associated with significant symptoms that respond to adequate therapy (Polo et al. 1988, Polo 1992, Anttalainen et al. 2007b).

IRR is an abnormal breathing episode consisting of prolonged episodes of non-periodic obstructive hypoventilation. The duration of one IRR episode is much longer than that of an apnea or hypopnea episode, ranges from 1 to 30 minutes. Episodes of IRR are characterized by gradually increasing intrathoracic pressure variation (Polo et al. 1991). Prolonged IRR episodes are also often associated with sustained arterial oxyhemoglobin desaturation and hypercapnia, after which the episode is terminated by movement arousal (Rauhala et al. 2007). Periods of IRR recorded with the SCSB reflect partial upper airway obstruction during sleep (Polo 1992).

In the UARS there is increased negative esophageal pressure during inspiration, which is recorded with an esophageal pressure catheter (Guilleminault et al. 1993). Since an esophageal catheter has not been used in PSG-studies to compare the esophageal pressure during apnea or hypopnea, the relationship between these physiological phenomena is unknown (Bao and Guilleminault 2004). In contrast, the esophageal pressure variation during the various SCSB breathing patterns has been recently measured (Tenhunen et al. 2010).

Inspiratory flow limitation is a common concept in the literature describing non-apneic SDB. Flow limitation is abnormal inspiratory flow which can be detected with a pressure sensor connected to a nasal cannula. A constant plateau-like shape in the middle part of the inspiratory flow curve is characterized by gradually decreasing inspiratory volumes, and constitutes a sign of non-periodic partial upper airway obstruction during sleep (Aittokallio et al. 2001). Inspiratory flow limitation is recorded in the CPAP devices and used for automatic titration of the appropriate pressure levels to control the episodes of OSA or partial upper airway obstruction during sleep.

### **2.2.3. Periodic leg movements in sleep**

Many patients with SDB have episodes of periodic leg movements (PLM). PLM are in patients with the restless legs syndrome (RLS) but they are also common in asymptomatic subjects. PLM should always be recorded together with respiration, since an interaction between respiratory abnormalities and leg movements is common. PLM or periodic movements in sleep (PMS) are repetitive movements of the lower extremities that may cause arousal from sleep and induce episodes of apnea or hypopnea (Hornyak et al. 2006). The presence of PLM episodes may disturb the diagnostics of breathing abnormalities. Although PLM can be observed also in healthy subjects, PLM appear more often and disturb sleep of patients with any degree of severity of SDB (Chervin 2001, Kapsimalis and Kryger 2009). When SCSB is used to record PLM, the findings

are regarded as positive for PLM if a series of at least four consecutive (interval 5-90 s) movements lasting 0.5-5 s are present during each epoch (Rauhala et al. 1996).

### **2.3. Pathophysiology**

The pathophysiology of SDB is not fully understood. The simultaneous changes in the control of sleep, breathing and the upper airway patency are a complex interactive process. Abnormal sleep is characterized by hypoventilation which raises the partial pressure of carbon dioxide (CO<sub>2</sub>) in the blood. There is also decreased muscle tone, which requires recumbent body position. All these factors predispose to SDB in particular when associated with obesity, structural abnormalities of the upper airway, ethanol ingestion or use of hypnotics.

The upper airway extends from the nostrils to the larynx and constitutes a ventilation tube surrounded by rigid and soft tissues. This tube serves the physiologic functions of deglutition, phonation and respiration. Partial narrowing or complete obstruction of the upper airway during sleep may be due to declining neuromuscular dilating control, modified upper airway reflex activity or the effect of gravity, especially in the supine position (Douglas and Polo 1994, Isono et al. 1997, Malhotra et al. 2000, Malhotra et al. 2004). There is also evidence of general neuronal imbalance and a decreased number of dendrites in the upper airway walls, which causes unsynchronised muscle function and decreases the natural dilatation capability of the airways (Edström et al. 1992, Friberg et al. 1998, Svanborg 2005). These changes may be the result of snoring, constant trauma caused by vibration of the soft tissues, recurrent inflammation or hypoxic stress (Puig et al. 2005, Gozal and Kheirandish 2006).

Extensive edema in the uvulopalatal region is one of the histological findings among OSAS patients (Woodson et al. 1991, Hamans et al. 2000, Berger et al. 2002), and the trauma caused by snoring to the tissues can cause airway edema (Puig et al. 2005). The mechanical trauma of SDB may cause connective tissue loosening and lead to instability between the epithelial and subepithelial tissue of the upper airway (Paulsen et al. 2002). Similar tissue loosening may also associate with increased tendency for SDB by aging. Morphological studies of tissue samples obtained from obese OSAS patients have reported fat tissue deposition in the uvula and soft palate (Stauffer et al. 1989, Zohar et al. 1998). Several anatomical factors contributing to the upper airway narrowing during sleep have been reported in patients with SDB (Partinen et al. 1988a, Horner et al. 1989, Shelton et al. 1993, Schellenberg et al. 2000, Liistro et al. 2003). A structural upper airway narrowing may be caused by nasal obstruction, macroglossy, palatal tonsil hypertrophy and elongation of the uvulopalatal region, extended distance of mandibula and hyoid, fat tissue deposition in adjacent structures and deformity or disproportion of the facial skeleton.

In addition to these pathophysiological factors related to excessive extraluminal pressure, the tendency of the upper airway to collapse may be even higher due to intraluminal

forces. During inspiration a negative intraluminal pressure is generated, following Bernoulli's principle, and related exponentially to airflow velocity (Gobrecht 1970). During inspiration the dynamic effect of suction is the highest within the narrowest section of the airway. Therefore, upper airway collapse is most likely to occur around the area where the upper airway is structurally narrowest. To maintain adequate ventilation forced inspiratory efforts and an elevated inspiratory pressure level are needed (Polo et al. 1991). When airflow is momentarily markedly reduced or zero due to airway collapse (near or together stretched walls of the upper airway), the elastic properties of the airway walls return to an open neutral position as airflow ceases or inspiratory phase ends. Once the airflow is reactivated during the inspiration after airway opening, a new similar breathing cycle follows. Repeated flow-limited respiratory cycles lead to prolonged episodes of IRR or periodic breathing (Remmers et al. 1978, Suratt et al. 1983, Polo et al. 1991).

The primary cause of SDB is unknown. SDB manifests only during sleep but the trigger of SDB is mainly related to anatomically predisposing factors (Malhotra et al. 2000). Whether the ultimate reason for the narrowing of the upper airway is adjacent tissue flaccidity or not is not certain. SDB probably results from multiple simultaneously present factors: edema caused by negative suction pressure, age-related decreased elasticity, vibrating trauma which activates degeneration of connective tissue and inflammatory hypertrophy of adjacent tissues. All factors leading to increased upper airway resistance during sleep may induce a self-aggravating process which results in partial or total obstruction along with increasing tissue flaccidity of the pharyngeal walls (Polo et al. 1991).

#### **2.4. Risk factors**

The main risk factors for OSA are obesity, male gender and decreased patency of the upper airway for obstructive anatomical reasons (Partinen et al. 1988a, Young et al. 1993, Kapsimalis and Kryger 2002). The OSAS may also develop over time in subjects who are not overly obese or old, as shown by long-term follow-up study of untreated SDB patients (Lindberg et al. 1999). Further, the duration and incidence of apnea in untreated mild to moderate OSAS patient progresses over time regardless of the patients age or weight (Svanborg and Larsson 1993, Pendlebury et al. 1997, Sahlman et al. 2007). However, aging has also been shown to present higher prevalence of SDB after 60 years age when compared to middle-aged population (Bixler et al. 1998, Bixler et al. 2001, Durán et al. 2001).

Central obesity of OSAS patients leads to a reduction in the total lung volume and functional residual capacity. This results in impaired ventilation and hypoxemia, as the breathing cycles utilize nearly the residual capacity of the lungs (Stein and Miller 1980). Excess body weight is the main single risk factor for SDB (Young et al. 1993, Durán et al. 2001). This finding is supported by the finding that weight gain among patients

with SDB increases AHI (Peppard et al. 2000), while weight loss decreases AHI (Rajala et al. 1991, Lojander et al. 1998a, Tuomilehto et al. 2009). Although women are more often obese than men, the prevalence of SDB is higher among men (Kapsimalis and Kryger 2002). This may be related to the finding that AHI correlates best with upper body obesity regardless of body mass index (BMI, kg/m<sup>2</sup>). This is also reflected in the finding that men with similar waist circumference and BMI seem to have greater degree of upper-body obesity, a smaller hip circumference and thicker subscapular skinfold (Millman et al. 1995). Magnetic resonance imaging (MRI) studies have shown that men have higher proportion of fat tissue in their neck area than women with a similar BMI (Whittle et al. 1999).

Some patients with extreme obesity develop hypercapnic respiratory failure, a condition also known as obesity hypoventilation. The Pickwick syndrome combines heavy snoring, sleepiness, obesity, nocturnal hypoventilation and heart failure (Burwell et al. 1956). Episodes of OSA were first described in patients with the Pickwick syndrome, but later on it was understood that OSA may occur also in patients without the Pickwick syndrome. Partial upper airway obstruction during sleep is a potential trigger for developing obesity hypoventilation, since it predisposes the heavy snorer to nocturnal CO<sub>2</sub> retention (Rauhala et al. 2007).

The higher prevalence of OSAS among men diminishes with age, but the reason for this is not clear (Strohl and Redline 1996, Tishler et al. 2003). Interestingly, while males have larger upper airway dimensions than females, males have a relatively higher breathing resistance at the pharyngeal level (White et al. 1985). This may be explained by the findings that females seem to have less collapsible and more consistent upper airway than males, despite their smaller upper airway lumen (Mohsenin 2001, Jordan et al. 2005). In females the menopause is a significant risk factor for OSAS, as the prevalence after menopause is approximately four times greater than before (Bixler et al. 2001). In addition to the anatomical factors predisposing to OSAS (Partinen et al. 1988a, Horner et al. 1989, Schellenberg et al. 2000, Liistro et al. 2003), heredity may also be involved in patients with OSAS (Douglas et al. 1993). If an OSAS patient is a first-degree relative, the risk of OSAS is doubled, possibly to some degree due to awareness of symptoms (Gislason et al. 2002, Sundquist et al. 2008). Secondary inflammation of the mucosal membrane of the upper airway may be due to smoking, alcohol consumption or gastroesophageal reflux (Remmers 1984, Wetter et al. 1994, Friedman et al. 2007a).

## **2.5. Assessment of sleep-disordered breathing**

### **2.5.1. Polysomnography**

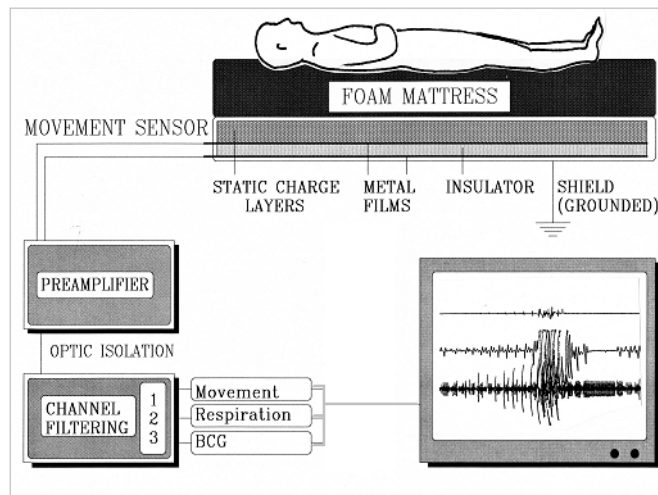
The diagnosis of OSAS requires objective demonstration of episodes of apnea or hypopnea during sleep. For this purpose, airflow, respiratory efforts and SaO<sub>2</sub> are measured as part of the PSG, in addition to electroencephalography (EEG),

electrooculography (EOG) and electromyography (EMG). These measurements allow determination of the sleep stages and cortical arousals. PSG may also include long-term monitoring of other biosignals, e.g., esophageal pressure variation, electrocardiography (ECG), transcutaneous or end-tidal CO<sub>2</sub> or body position (American Sleep Disorders Association 1997). Although the full PSG is the golden standard for diagnosing SDB and is strongly recommended in the USA (Epstein et al. 2009), simple and more cost effective approaches for establishing the diagnosis have been developed, particularly in Europe. Arguments against PSG have underscored the importance of measuring the sleep quality, arousals during sleep and treatment follow-up. The PSG-derived AHI has been criticised as being an insufficient estimation of the symptoms and signs of nonapneic SDB and of the severity of upper airway dysfunction (Hudgel 1986, Flemons and McNicholas 1997, Cracowski et al. 2001). The simplified cardiorespiratory recordings not requiring the full PSG have been promoted to enable screening of larger populations.

### **2.5.2. Static Charge-Sensitive Bed (SCSB)**

The SCSB was the earliest Finnish version of a simplified cardiorespiratory monitoring system for diagnosing SDB (Alihanka et al. 1981, Alihanka 1987). This method gained marked popularity in Finland because of its non-invasive nature and low cost. SCSB never became widely used outside of Finland, because the prevailing paradigm of SDB did not accommodate new concepts such as partial upper airway obstruction during sleep (Polo 1992). Many studies have used the standardized SCSB scoring principles in combination with oximeter recordings as stand-alone devices (Polo et al. 1991, Kirjavainen et al. 1996a, Lojander et al. 1998b, Anttalainen et al. 2007b) or have combined SCSB to PSG (Polo et al. 1988, Polo et al. 1989, Polo et al. 1992, Kirjavainen 1996b). A detailed description of the SCSB scoring principles are presented in the literature (Polo et al. 1988, Polo 1992, Anttalainen 2007a) and in the methods section (4.2.1) of this thesis.

The SCSB is a non-invasive, validated method for monitoring body movements, heart beats and breathing (Alihanka et al. 1981, Polo 1992). The movement sensor with static charge layers on the top of it is located under a standard foam mattress (Figure 1). All movements of the patient change the status of the static charge layers and produce an electric charge which is conducted to a flexible metal film layer. Beneath this layer, insulated from the layer above, is a shield-grounded second metal film layer. The resulting electric potential differences between the capacitor plates are first preamplified and then filtered into three different frequency bands: 0.25-0.9 Hz for breathing, 0.3-16 Hz for gross body movements and 6-16 Hz for the heart beats.



**Figure 1.** Setup for a SCSB recording: movement sensor derived original signals are amplified and filtered by frequency into gross body movements, respiratory movements and heart beats, i.e. ballistocardiogram (BCG). The polygraph is analyzed by inspection (reprinted with permission from Polo et al. 1992).

Diagnosing SDB with the SCSB is not based on measurement of airflow but on identification of various patterns of respiratory drive. This is of particular clinical importance, since the respiratory drive predicts the subjective symptom of sleepiness better than the AHI (Pelin et al. 2003, Svensson et al. 2008). Detection of partial upper airway obstruction during sleep with the SCSB in symptomatic patients with an AHI below 5/hour may thus relate to the patient's symptoms and indicate therapy (Polo et al. 1988, Anttalainen et al. 2007b). Due to the limitations of PSG, the use of SCSB is more feasible among patients presenting not only with obstructive apnea during sleep but also with partial upper airway obstruction as the primary finding. With the SCSB, breathing can be monitored with the least possible disturbance to sleep, since no electrodes are attached to the subject. In addition to monitoring of the breathing pattern, the SCSB shows motor activity, such as PLM as well as heart beat in bed (Rauhala et al. 1996).

The basic distinction of abnormal respiratory drives is between periodic breathing and non-periodic breathing (Anttalainen et al. 2007a). The frequencies of various SCSB patterns are expressed as the percentual amount of time in bed (TIB), not as events per hour of sleep (/h). Despite different time bases, the SCSB derived prevalence of obstructive breathing patterns and the PSG-derived AHI-indices are comparable (Polo 1992, Anttalainen 2008).

### 2.5.3. Severity assessment of sleep-disordered breathing

According to the guidelines of the Institute for Clinical Systems Improvement, the severity of OSA is divided into mild (AHI 5-15/h), moderate (AHI 16-30/h) and severe (AHI >30/h) forms (Institute for Clinical Systems Improvement 2008). Estimation of

the severity of OSA is based on the PSG findings, a sleepiness symptom questionnaire and the frequency of arterial oxyhemoglobin desaturations. The Epworth Sleepiness Scale (ESS) score is the most used questionnaire to evaluate the probability of falling asleep at daytime (Johns 1992). ESS has a tendency to increase simultaneously with AHI independently from age or sex according to studies where patients have analyzed their symptoms with questionnaires (Young et al. 1993, Gottlieb et al. 1999).

Since the late 1990's a working group consisting of experts from different clinics has worked to determine the diagnostic and treatment rules for adult sleep apnea patients in the Turku University Central Hospital district (VSSHP Hoitoreitit, Uniapnea). According to these rules, the diagnosis of OSA requires 5/h or more breathing abnormalities, e.g., apnea or hypopnea, and for partial upper airway obstruction during sleep 5% of TIB or more of IRR or periodic breathing without apnea, during a sleep study. Severity is estimated according to adapted guidelines of the Institute for Clinical Systems Improvement (Table 2). The major difference is that our hospital guidelines include partial upper airway obstruction during sleep into the severity estimation. Therefore, symptomatic patients may get diagnosis and treatment irrespective of their AHI, provided that partial obstruction is objectively demonstrated in the sleep recording. Long-term therapy of SDB is warranted if a therapeutic trial with CPAP, an oral appliance or other forms conservative treatment gives total or partial relief of these specific symptoms (VSSHP Hoitoreitit, Uniapnea).

**Table 2.** Clinical severity classification of SDB (VSSHP Hoitoreitit, Uniapnea).

SEVERITY OF SDB	AHI (/h)	SaO <sub>2</sub> (%)	SLEEPINESS
<b>MILD</b>	AHI ≤ 15	SaO <sub>2</sub> mean ≥ 90 <i>and</i> SaO <sub>2</sub> min ≥ 85	Sleepiness is present only when person is inactive or when little attention is required, and may not be present daily (sitting etc.) Such sleepiness causes minor social or occupational impairment
<b>MODERATE</b>	16 ≤ AHI ≤ 30	SaO <sub>2</sub> mean < 90 <i>and</i> SaO <sub>2</sub> min ≥ 70	Sleepiness is present daily when person is minimally active and a moderate degree of attention is required (watching tv etc.)
<b>SEVERE</b>	30 < AHI	SaO <sub>2</sub> mean < 90 <i>or</i> SaO <sub>2</sub> min < 70	Sleepiness is present daily when person is active or concentrating into tasks that are requiring significant attention (driving etc.) Such sleepiness causes major impairment of social or occupational function

## 2.6. Determination of the level of upper airway obstruction

Evaluation of the upper airway of SDB patients and identification of the specific level or levels of narrowing causing partial or complete obstruction are essential if surgery is



considered. Several techniques and classifications have been introduced in the literature to predict successful surgery.

*The clinical state* identifies three different levels of upper airway obstruction during sleep: isolated retropalatal (type I), isolated retrolingual / hypopharyngeal (type III) or combined (type II) obstruction, with further division into oropharyngeal (type IIa) and oro-hypopharyngeal (type IIb) obstruction (Fujita 1987, Fujita et al. 1991, Fujita 1993). Samsoun and Young introduced a four degree staging system (Samsoun-Young classification); modified by Mallampati (Mallampati et al. 1985), for evaluation of the width of the tongue in proportion to the oroantral dimension between posterior palatine arches (Samsoun and Young 1987). Friedman and colleagues presented a four level classification system based on the size of the palatine tonsils and the tongue position at clinical examination (Friedman et al. 2002, Friedman et al. 2004a). Their staging included three levels based on clinical oral findings and BMI. They also classified patients as having mild, moderate, moderate-severe or severe OSAS by preoperative AHI-values. An anatomical staging system before UPPP predicts a better success rate of surgery than OSA severity assessment (Friedman et al. 2005, Li et al. 2006). There are also other different measurements used for analyzing the laryngoscopic view, the neck circumference, mandibular protrusion and overbite, cricomental space, thyro-rami and sterno-mental distance, and thyromental and sterno-mental displacement.

*The Müller manoeuvre* relies on the classification of Sher and colleagues (Sher et al. 1985). This manoeuvre yields four degrees of airway narrowing, ranging from minimal to complete obstruction at three endoscopical levels, i.e., supraglottic, uvular tip and nasopharynx. The manoeuvre is performed under forced inspiration against a closed mouth and compressed nostrils when the patient is awake. For prediction of successful surgery this method does not present significant value at the soft palate level (Boot et al. 1997, Hsu et al. 2007). However, Müller manoeuvre can be helpful identifying clear hypopharyngeal or epiglottic level obstruction as well as evaluating situations where primary surgery has not been successful (Catalfumo et al. 1998).

*Videoendoscopy* during spontaneous sleep was first evaluated for describing palatopharyngeal or tongue level collapse during respiration phases of OSAS patients with hypersomnia (Borowiecki et al. 1978). Because of the videoendoscopy moment captured is limited to a short follow-up period and because measuring requires work at night, videoendoscopy under sedation is usually used. Videoendoscopy is accurate for detecting or excluding supraglottic or glottic narrowing (Golz et al. 2000). Isolated narrowing of the tongue base, the epiglottis or soft palate or a combination of these can be classified with videoendoscopy. However, this method performed under sedation does not necessarily predict successful surgery at velopharyngeal level (Hessel and Vries 2004). The use of endoscopy or videoendoscopy requires individual consideration of each patient (Stuck and Maurer 2008).

*Radiographic cephalometric* data have shown that some OSAS patients have anatomic risk factors, such as long and thick soft palate together with a reduced minimum retropalatal

airway width, long distance from the hyoid bone to the mandible plane, retroposition of the upper and lower jaw, micrognathia or elongation of the mid-facial height. Radiographic cephalometry is of great value primarily when used for maxillofacial and mandible surgery and it is the standard diagnostic tool when oral appliances are inserted (Hochban et al. 1994, Stuck and Maurer 2008). Still, radiographic cephalometry is not used as a standard method to predict the outcome of UPPP (Boot et al. 1997, Liu et al. 2005).

*Digital fluoroscopy* provides dynamic imaging of the entire upper airway contour in two-dimensional lateral fluoroscopy views over the course of several respiratory cycles. Digital fluoroscopy has shown that there is less collapsibility at the soft palate level after surgery among the OSAS patients who respond well to UPPP with laser (Tsushima et al. 1997). A technique presenting similar type of radiographic setting, called videoradiography, can also be used to determine the level and type of apnea in OSAS patients, although the actual degree of OSAS and the mean duration of apnea cannot be fully estimated (Hillarp et al. 1996). The technique has shown that the velopharyngeal level airway is more collapsible preoperatively among SDB patients when compared to controls with no sleep disorders (Tsushima et al. 1996). Successful surgery at the velopharyngeal level could not be predicted preoperatively, but an inferior position of the hyoid bone was a predictor of a poor surgical result (Tsushima et al. 1997). Digital fluoroscopy cannot be used for assessment of sleeping patients for long periods, due to the requirement that the patient must lie supine throughout scanning. As a balance, the ionizing radiation exposure is minor when compared with dynamic computed tomography imaging. A detailed description of digital fluoroscopy is presented in the literature (Tsushima et al. 1996, Tsushima et al. 1997), and in the methods section (4.2.5) of this thesis.

*Computed tomography* (CT) of the upper airways of OSAS patients has demonstrated an increased tissue volume at the base of the tongue and palatal areas. This leads to narrowing of the hypopharyngeal level and to significant obstruction of the retropalatal cross-sectional area (Schwab et al. 1993). There are probably structural factors determining whether the patient has either partial or complete upper airway obstruction during sleep. In patients with OSAS the upper airway is narrower at the soft palate level, while patients with partial obstruction have narrower airways at the tongue base and hyoid bone levels (Polo et al. 1991). Dynamic and ultrafast CT has been used to show that there are substantial changes during a respiratory cycle: patients with SDB have a narrow cross-sectional area and increased collapsibility at the velopharyngeal level (Yucel et al. 2005). Both UPPP and uvulopalatal flap increase the postoperative retropalatal space according to scanning findings (Shepard and Thawley 1989, Li et al. 2005). Small upper airway dimensions identified before surgery predict successful UPPP in OSAS patients (Ryan et al. 1991). Here, radiation exposure, assessment during sleep and the need for a constant supine position of the patient during scanning are unresolved challenges.

*Magnetic resonance imaging* has demonstrated excessive fat tissue deposits in the collapsible areas surrounding the upper airways in obese OSAS patients (Horner et

al. 1989), and especially in the anterolateral part to the upper airway with or without obesity (Mortimore et al. 1998). In addition to this finding, also increased volume of tongue and lateral pharyngeal walls are a risk factor for developing OSA (Schwab et al. 2003). Dynamic imaging has presented data about the specific site of obstruction in patients sleeping supine, and this data is helpful for determining the appropriate therapy for OSAS patients (Yoshida et al. 1999). However, this technique has not been shown to predict successful surgery at the velopharyngeal level and the need for a constant supine position of the patient may limit its value.

*Multi-channel pressure measurements* have been developed from single measuring point catheters, which detected obstructions at various levels of the upper airways of OSAS patients by moving the measuring point of catheter (Hudgel et al. 1984). Findings from recordings of multi-channel pressure catheters and PSG have demonstrated that pressure measurements are very sensitive and specific for identification of apnea and hypopnea (Tvinnereim et al. 1995). Thin multi-channel pressure transducers can be used to detect preoperatively palatal obstruction before soft palate surgery (Skatvedt et al. 1996). Patients with predominantly transpalatal obstruction have a higher rate of reduced apneas after UPPP than those with subpalatal obstruction (Osnes et al. 2002). The success rate of surgery at the soft palate level can be improved by selecting patients with multi-channel pressure measurement, but a prerequisite for success is accurate positioning of the catheter. The results of this type of examinations must be balanced against the risk of disturbed sleep quality caused by method itself.

*The critical closing pressure* was first described as a measure of airway collapsibility among apneics (Smith et al. 1988). The pressure needed for keeping the upper airway open must exceed a certain pressure, the critical closing pressure, caused by obstructed or narrowed upper airway. The nasal CPAP device must produce positive pressure levels as needed to maintain breathing through open airways. In healthy individuals this pressure is less than -8 mbar and in OSAS patients above 0 mbar during sleep phases with obstruction (Gleadhill et al. 1991). The critical closing pressure is a valuable measure of upper airway patency of patients who have undergone surgery, but there is no evidence of its usefulness for the preoperative evaluation of OSAS patients, because the identification of a specific obstruction level is unknown as respiratory airways cannot be divided into parts.

The control of upper airway patency during sleep is very different from the control when awake. Therefore, the value of studies performed under sedation or when the patient is awake is questionable. The same is true for measurements taken during short periods of sleep and for measurements with ionized radiation exposure. Despite well defined techniques, it has been difficult to determine the level of obstruction because of poor repeatability, examiner variability and a lack of standard scoring systems. However, evaluation of the upper airway does reveal irreversible anatomic changes, which may be a cause for obstruction or a consequence of upper airway narrowing during sleep. There is only limited evidence that identification of obstruction actually improves the

success of surgery. Anatomical classifications based on clinical examination seem to be the single most important method to identify sites of obstruction of relevance for predicting the surgical success of SDB patients.

## **2.7. Surgical success rate of Sher**

*The success rate of Sher*, advocated by Sher and colleagues, has been widely used for estimating the efficacy of operative treatments of patients with OSAS (Sher et al. 1996). Often, the AHI score is 5/h or more postoperatively which implies that the patient has apneas despite surgery. This caused several authors to use various criteria for surgical success assessment based on PSG findings, oxyhemoglobin values or symptom questionnaires. This discrepancy made comparison between different study groups' results difficult. Sher and colleagues conducted a meta-analysis and presented the concept of surgical success rate of Sher (Sher et al. 1996). Surgery is considered successful if an individual postoperative AHI value is less than 20/h and the AHI is reduced at least by 50% (or AHI < 10/h instead of 20/h if the preoperative value is less than 20/h). The number of patients fulfilling this criterion of success is divided by the total number of operated patients and presented as percentage (Sher et al. 1996). A threshold value of AHI was set at less than 20/h and this was based on a finding from a study by He and colleagues: 385 OSAS patients were followed for eight years and the mortality among patients presenting with an apnea index greater than 20/h was 40% and zero in patients with an apnea index of less than 20/h (He et al. 1988). The criterion of a reduction of AHI with 50% or more compared to the preoperative value comes from a study by Fujita and colleagues as their criterion for surgical response (Fujita et al. 1981). The Sher value is assessed according to the apnea and hypopnea detected with PSG. Because respiratory cessations recorded with PSG during sleep are most important for diagnosing SDB, the basis of the Sher value is clinically more relevant than SaO<sub>2</sub> values or symptom scores, which result from SDB. There are also other definitions for treatment success in a review article analysing problems in UPPP research (Megwalu and Piccirillo 2008). All studies included into this review are based on the AHI and if not using the success rate of Sher they mostly are defining success as AHI less than 20/h or 10/h according to preoperative AHI. However, the aim of all treatments, including surgery, has been to achieve a postoperative AHI less than 5/h and the disappearance of symptoms.

## **2.8. Conservative treatment of sleep apnea**

### **2.8.1. Lifestyle modifications**

The avoidance of various drugs that affect the central nervous system and alcohol is essential for maintenance of a sufficient sleeping hygiene and sleep quality (Scanlan et al. 2000). Use of these drugs and alcohol tends to increase weight and this impacts OSA negatively. Partial or complete obstruction occurring mainly or exclusively in the supine position during sleep is a situation where upper airway is probably narrowed at

the retrolingual level. In these position-dependent forms of obstructive apnea avoidance of supine position during sleep relieves obstruction (Neill et al. 1997).

Most patients with OSAS are obese (Malhotra and White 2002). It has been shown that even in the absence of a previous diagnosis of sleep apnea the prevalence of OSAS among patients with morbid obesity (BMI > 40 kg/m<sup>2</sup>) is around 80% among males and 50% among females (Salvador et al. 2004, Fritscher et al. 2007). On the other hand, 70% of OSAS patients are obese and thus the obesity is a two-perspective dilemma in the case of OSAS (Malhotra and White 2002). Therefore, the treatment should always aim at weight loss in case of obesity.

OSAS patients with severe overweight benefit from a hypocaloric diet and induced weight loss in terms of decreased arterial oxyhemoglobin desaturations (Kansanen et al. 1998). In obese patients with mild OSAS weight loss reduces episodes of obstructive apnea as the only treatment (Barvaux et al. 2000, Peppard et al. 2000). Nerfeldt and colleagues have shown that parameters related to respiration as well as to sleep tend to improve in obese patients with OSAS after reduction of BMI (from 40 to 35 kg/m<sup>2</sup>) following active dietary intervention (Nerfeldt et al. 2008). After a six-month study period 27% of patients enrolled in their trial had a reduction in AHI of at least 50% and under 20/h. This beneficial effect was lost after two years of follow-up, as the success rate had fallen to 15% and the change in AHI was no longer significant (Nerfeldt et al. 2010). Tuomilehto and colleagues have shown that less obese patients with milder OSAS benefit from a very low calorie diet and lifestyle counselling (Tuomilehto et al. 2009). In their one year follow-up study AHI was reduced from 10 to 6/h in concert with a reduction of the BMI from 33 to 30 kg/m<sup>2</sup> and the results for these two parameters were better for diet combined to counselling when compared to counselling only. A longitudinal population study on behavioural weight loss has shown that there is a 3% decrease in AHI for every 1% loss of body weight (Magalang and Mador 2003). However, there is no strong evidence for the efficacy of lifestyle modifications for OSAS patients due to lack of adequate studies. Weight reduction of obese persons has a positive overall impact on health (Shneerson and Wright 2009).

Two prospective studies on bariatric surgery imply that apnea episodes are reduced after weight loss (Fritscher et al. 2007, Lettieri et al. 2008). Both studies considering, an average BMI decrease from 53 to 28 kg/m<sup>2</sup> reduced AHI from 44 to 24/h by 55% in more than 50% of patients when counting results in proportion together. Bariatric surgery for the treatment of obesity is thus an option for treating OSAS if weight loss cannot be achieved by other means (Buchwald et al. 2004).

### **2.8.2. Continuous positive airway pressure**

The first line treatment for mild to severe OSA is nasal CPAP (American Thoracic Society/American Sleep Disorders Association 1998). The pressure produced by a CPAP ensures that the obstruction sites in the patient's airways are continuously open. CPAP allows sufficient inspiration and expiration and may stimulate the pulmonary receptors leading to pharyngeal muscle dilatation in the airways (Sullivan et al. 1981, Issa and Sullivan 1984).

OSAS patients with mild symptoms adhere poorly to nasal CPAP (Engleman et al. 1999, Rosenthal et al. 2000, Yetkin et al. 2008). Nasal CPAP is less effective in patients with mild OSAS than in patients having moderate or severe OSAS (Barnes et al. 2002, Patel et al. 2003). In cases of partial upper airway obstruction during sleep, diagnosed with SCSB, the adherence to nasal CPAP therapy after one year use was 58% (average 5h/night), and was comparable to patients with predominantly conventional periodic obstructive apnea (Anttalainen et al. 2007b). Interestingly, when OSAS patients with a high AHI ( $\geq 30$ /h) but who had no symptoms were treated with CPAP or sham CPAP there was no significant differences in ESS, adherence to CPAP use, AHI or saturation levels between the groups over time (Barbè et al. 2001). This finding suggests poor biological benefit from CPAP; understandably, patients with no symptoms before treatment are poorly motivated to treatment and this predicts poor adherence. This finding supports the thinking that it is the symptoms rather than the AHI that needs to be treated.

In contrast to some previous studies, active use and high compliance with nasal CPAP treatment are predicted by older age, more severe apnea, high AHI-value, increased daytime sleepiness and significant symptom relief due to treatment (Engleman and Wild 2003). Compliance with nasal CPAP in the short-term is over 90% but is reduced in long-term use ( $>1$  year) to 29-86% and is, generally, around 70% (Meslier et al. 1998, McArdle et al. 1999, Grote et al. 2000). As the average AHI in most studies with OSAS patients is below 5/h which is considered to signify cure following CPAP treatment, the overall success rate of CPAP could be the same as the long-term compliance rate, i.e., 70%. Common practice defines clinically sufficient use of CPAP as  $\geq 4$  hours per night (Weaver and Grunstein 2008). Three hours or more per night has been considered as the threshold usage for positive compliance (McArdle and Douglas 2001). Thus, assuming that the average sleeping time in bed is 7-8 hours per night, a significant part of the sleeping time is still outside the reach of nasal CPAP and this impacts on the overall nocturnal AHI value. If Sher's criteria are applied, the success rate for CPAP would be even lower than 70%, because the average AHI is derived from the time of active CPAP use only. By taking into account the total sleeping time the period without appliance results in decreased levels of  $\text{SaO}_2$  due to increased appearance of SDB periods.

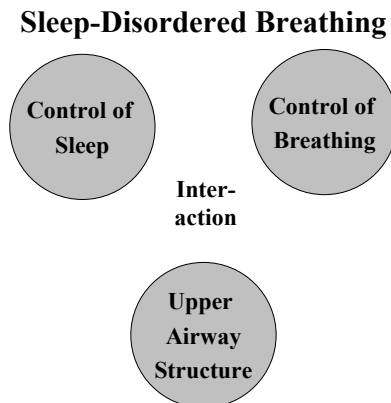
The patients' tolerance to CPAP treatment has improved with recent advances in mask materials and humidifiers, and the device itself, since it has become possible for patients to choose bi-level positive airway pressure (Bi-PAP). Bi-level ventilators deliver inspiratory pressure support in addition to CPAP, which makes it especially suitable for obese OSAS patients with restrictive lung wall disease or congestive heart failure. Determination of a suitable pressure level can be made during monitoring with the help of automatic positive airway pressure (auto-PAP) under domestic conditions. For home-use, this device is helpful for OSAS patients who need variable pressure in synchrony with a changing lung capacity (Guilleminault and Abad 2004).

The compliance of patients with conservative treatments like CPAP or oral appliances is poor in the long-term due to decreased utilization time. Often OSAS patients even reject

these treatments. Surgery, in contrast, aims to reach a permanent therapeutic result without the need for external devices by repairing obstructive sites in the upper airways. However, CPAP is the treatment of choice in OSA, and all surgical procedures should be made only after careful consideration of expected benefit to the individual patient. This prudence is also in order when new treatment concepts are introduced for OSA in the future.

## 2.9. Surgical treatments

SDB is a complex interaction between the state of sleep, abnormal control of breathing and abnormal upper airway structure (Figure 2). All these factors contribute to SDB. For instance, sleep deprivation for any reason induces more SDB through increased upper airway muscle relaxation (Douglas and Polo 1994). Also, heart failure causes abnormal breathing control resulting in periodic or Cheyne-Stokes breathing (Naughton 1998). This may further induce secondary functional upper airway obstruction. A structurally narrow upper airway from the nares to the trachea may cause significant functional problems during sleep. Upper airway surgery targets only this last component. In most cases, however, all these components are involved in the pathogenesis of SDB. The benefit that can be expected from surgical intervention depends on the degree of anatomic narrowing, how this contributes to SDB and how much that component can be relieved by surgery. Surgical modifications of the upper airway for OSA have recently been reviewed (Caples et al. 2010) and guidelines for the upper airway surgery in OSA have been presented by the American Academy of Sleep Medicine (Aurora et al. 2010).



**Figure 2.** Several factors contribute to the manifestation and severity of SDB. Surgery targets only the upper airway structure.

### 2.9.1. Uvulopalatal surgery

The uvulopalatal region was an early target for surgery attempting to relieve airway obstruction during sleep. There were records of striking structural abnormalities in patients who had had severe OSAS for many years. These included a widened and /or

elongated uvula and an excessive mucotic membrane of the palatine arches, hypertrophy of tonsillar adenoids or a reduced retropalatal space due to skeletal abnormalities. More than one of these predisposing anatomical abnormalities may contribute to obstruction.

Several surgical techniques have been used to treat OSAS patients. These surgical procedures produce only single-level relief in the superior part of the pharynx, but in moderate and severe OSA the obstruction is assumed to be a multi-level problem. Therefore, especially after an era of surgery at the palatine level it has become evident that other obstruction sites are possible and must be taken into consideration if a postoperative sleep study does not show a sufficient response.

#### 2.9.1.1. Uvulopalatopharyngoplasty

The aim of UPPP is to remove palatal tonsils and retropalatal obstruction and advance the soft palate anteriorly. A large variety of surgical procedures have been published since the original technique of UPPP was introduced by Ikematsu in 1964, and later modified by Fujita and colleagues (Ikematsu 1964, Fujita et al. 1981). The operation consists of tonsillectomy and excision of redundant tissues from the free margin of the soft palate and the tonsillar pillars with some resection of uvula muscle (Pirsig et al. 1989). The posterior pillars in tonsil folds should be lateralized and the palatal musculature saved. There are several modifications of the original description of UPPP by Fujita, e.g., submucosal UPPP (Friedman et al. 2000a), the Fairbanks technique (Fairbanks 1999) and UPPP with preservation of the uvula (Han et al. 2005). However, also more invasive techniques of UPPP have been presented with transposition of the oropharyngeal muscles, as in the case of expansion sphincter pharyngoplasty (Saint Raymond et al. 2004) or lateral pharyngoplasty (Cahali 2003).

In a meta-analysis of UPPP, Sher and colleagues reported a success rate of 41% in an unselected population of patients with OSAS (Sher et al. 1996). However, in studies focused on obstruction at the velopharyngeal level alone, the short-term success rate was 52%. Most studies on the efficacy of UPPP are not prospective nor do they provide long-time follow-up, since the typical follow-up time has only been 3 to 12 months. There are three studies with both short-term and long-term follow-up after UPPP and they indicate that counted in proportion there are cured patients by Sher's criteria in 62% at seven months follow-up and 47% after five years (Larsson et al. 1994, Lu et al. 1995, Janson et al. 1997). Since UPPP loses effect over time, patients may require sleep studies as control still long after the operation.

Studies comparing UPPP with other treatments of OSA are needed, as effects of comorbidities, aging and other factors leading to apnea progression are partially unknown. In a study by Keenan and co-workers patients who had undergone UPPP had a similar survival fraction after five years (95%) as patients on CPAP (Keenan et al. 1994). This study did not evaluate outcome in terms of AHI or  $\text{SaO}_2$ , which would have described the severity of residual SDB after the operation. In a study by Lojander and colleagues a population of OSAS patients was randomized into two separate groups, UPPP (with or



without mandibular osteotomy) and CPAP (Lojander et al. 1996). A part of both treatment groups was further randomized into control patients. After 12 months of follow-up 62% of CPAP patients and 39% of UPPP patients had normal  $\text{SaO}_2$  during sleep. In both treatment groups the nocturnal saturation levels were higher and daytime fatigue lower than among controls. One may assume that patients in both intervention groups who had a positive response to treatments also had an AHI close to normal. There is evidence of decreased mortality after successful CPAP treatment of patients with OSAS (Marti et al. 2002). The impact of UPPP on long time survival has also been studied. OSAS patients treated with either CPAP or UPPP were included in a retrospective study with four years of follow-up (Weaver et al. 2004). In the CPAP treatment group, 7.1% died, but only 3.4% in the UPPP group. When the data was corrected for age, gender, initiation year of treatment and co-morbidities the mortality of UPPP patients was lower. However, the lack of AHI-values and data on the use of CPAP do not exclude the possibility that CPAP patients may have had more severe OSAS. In case of poor adherence to CPAP, UPPP remains a therapeutic alternative for patients with obstruction at the velopharyngeal level. Marti and colleagues focused on determining the impact of different treatments on the mortality of patients with severe OSAS (Marti et al. 2002). The overall mortality rates did not differ between the general population and any of the active treatments (UPPP, diet or nasal CPAP) during follow-up (5-7 years). However, only patients with OSAS and a BMI higher than  $35 \text{ kg/m}^2$  showed a trend towards increased mortality when compared with general population. Lysdahl and Haraldson compared the impact of UPPP on the mortality of OSAS patients with the impact of UPPP on heavy snorers without apnea and control population (Lysdahl and Haraldson 2000). There was no difference in relative mortality of OSAS patients, snorers or controls during the nine years of follow-up. The long-term cumulative survival rate was the same (>96%) in all groups. This finding corroborates the positive effect of UPPP on mortality in patients with OSAS, but it must be emphasized that patients undergoing UPPP usually have less severe OSAS and less cardiovascular co-morbidities than OSAS patients treated with nasal CPAP. Obviously, this circumstance hampers comparisons of the long-term outcome between the two treatment modalities.

Khan and colleagues analyzed the polygraphic sleep study data and BMI in their patients with OSAS treated with UPPP (Khan et al. 2009). There were no significant changes in BMI before and six months after UPPP and the changes in AHI did not correlate with the changes in BMI. The success rate of Sher was 51%, a figure similar to other long-term studies mentioned previously in this thesis. Of the patients from Khan and colleagues, 24% had a postoperative AHI of 5/h or less, and compared to the other patients from this study, these patients were younger and their mean preoperative BMI ( $31 \text{ kg/m}^2$ ) was also lower.

UPPP has been used in mild or moderate forms of OSAS as a single surgical procedure for non-obese ( $\text{BMI} < 30 \text{ kg/m}^2$ ) patients with isolated narrowing at the velopharyngeal level. In the case of patients with severe OSAS, a combination with other operative treatments, i.e. multi-level surgery, is preferable.

### 2.9.1.2. Uvulopalatoplasty

Laser uvulopalatoplasty (LUPP), a laser-assisted modification of the conventional UPPP technique, was introduced in 1986 by Carenfelt in Sweden for the treatment of habitual snoring (Carenfelt 1991). LUPP was performed under local anesthesia and sutures were used for advancing the possible scarification onto the oral side. Carenfelt compared the symptoms after UPPP with LUPP without tonsillectomy. There were no differences between these two groups in the short-term results, as 90% of patients in both groups considered that their snoring had improved. The benefits of LUPP were shorter operative time and faster convalescence compared to those in UPPP.

Hultcranz and colleagues performed a study of LUPP for the treatment of OSAS patients and removed the uvula and only redundant parts of the edge of the soft palate and the posterior pillars (Hultcranz et al. 1999). The posterior pillars were pulled anteriorly before suturing them together with the anterior pillars in the region of superior tonsil folds. The long-term (five years) effect of LUPP was evaluated with a questionnaire and PSG. Approximately 80% of patients experienced a positive effect on daytime somnolence and snoring, but side-effects, such as choking or globus, were reported by 40% of the patients during the first postoperative year. These complaints diminished over the years. In the study 80% of OSAS patients were responders after five years: their apnea reduction was more than 50%, and 50% of patients were classified as cured (apnea index 5/h or less). Hultcranz and colleagues concluded that LUPP has a good therapeutic effect in the long-term for selected OSAS patients.

The selected studies concerning LUPP in this thesis are presented in Table 3.

Skatvedt modified the technique of laser-assisted uvulopalatoplasty (LUPP) (Skatvedt 1996) from previously published techniques in Sweden (Lindholm et al. 1989, Carenfelt 1991). In contrast to conventional UPPP, Carenfelt and Skatvedt aimed primarily to save the palatopharyngeal muscles. Skatvedt reported that after an average of 18 months of follow-up the patients reported decreased symptoms and apneas (Skatvedt 1996). Only a part of the patients was studied with PSG after LUPP. These patients had only minor episodes of hypopnea and no apnea. In another study the same technique was used for LUPP also the level of obstruction was measured using catheter with pressure sensors before and after operation of OSAS patients (Skatvedt et al. 1996). Preoperatively the site of obstruction during sleep was located in the velopharyngeal segments in 90% of the patients presented with hypopnea or obstructive apnea. The postoperative AHI decreased with 65% (from 20 to 7/h) and 69% of the patients had a reduction in AHI of more than 50% at an average follow-up of seven months. A similar tendency toward improvement was reported by patients: they experienced less snoring, fewer apneas witnessed by other persons, less daytime sleepiness and a reduced tendency to fall asleep during daytime. Skatvedt and colleagues concluded that LUPP was appropriate when performed on patients whose obstruction is located in the velopharyngeal level. However, some patients still had residual obstruction after LUPP, which might have been due to a reduced distance between the hard palate and the posterior pharyngeal wall.

**Table 3.** Data from the selected studies concerning LUPP are presented. Results of these studies are based on the symptoms related to SDB and findings of PSG.

Reference	Treatment	n	BMI (before/after) (kg/m <sup>2</sup> )	Follow-up (months)	Diagnosis	Result
Carenfelt et al., 1991	LUPP vs. UPPP	63/37	-	3 - 4	snoring	90% of patients reported decreased snoring without differences between groups, but the time of convalescence and operative time were less with LUPP
Skatvedt, 1996	LUPP	100	25.7/25.7	3 - 18	OSAS/ snoring	a significant decrease among OSAS patients occurred in episodes of apnea and hypopnea, and similar decrease among all patients' subjective symptoms
Skatvedt et al., 1996	LUPP	16	27.3/27.4	3 - 16	OSAS	69% of patients were responders (AHI decreased with 50% or more) as the average AHI reduced from 20 to 7/h, there were also significantly less snoring, daytime sleepiness and other symptoms
Isberg et al., 1998	LUPP	79	25.4/ -	24	OSAS/ snoring	27% of patients reported persistent dysphagia (pharyngeal function of swallowing was deviant in 76% of these dysphagic patients) and decreased snoring in 79% and daytime sleepiness in 80%
Hultcranz et al., 1999	LUPP	19	27/ -	60 - 84	OSAS	80% of patients were responders (episodes of apnea decreased with 50% or more) and 50% of patients were cured (episodes of apnea 5/h or less)
Hagert et al., 1999	LUPP vs. UPPP	29/81	-	16 - 97	OSAS/ snoring	86% of patients reported decreased or none snoring after treatment, but no differences were seen between LUPP/UPPP (similar finding with daytime sleepiness)
Levring-Jäghagen et al., 1999	UPP (vs. LUPP)	76	26.1/ -	12 - 24	OSAS/snoring	29% of patients reported persistent dysphagia (Isberg et al. 1998: similar finding, but significantly less nasal regurgitation in LUPP) and reduced snoring in 96% and daytime sleepiness in 90%
Lysdahl and Haraldsson, 2002	LUPP vs. UPPP	60/61	26/26.6 vs. 27.9/28.4	60 - 96	snoring	persistent symptoms were reported in 27% of LUPP and in 36% of UPPP patients, snoring 64% and 46%, daytime sleepiness 35% and 30% (respectively)
Levring-Jäghagen et al., 2004	LUPP vs. UPPP	22/20	25.8/ - vs. 27.9/ -	12	snoring (±OSAS)	29% of patients reported persistent dysphagia (LUPP and UPPP did not influence the postoperative appearance of dysphagia) and reduced snoring in 93% and daytime sleepiness in 96%

Lysdahl and Haraldsson presented a long-term follow-up (5-8 years) of patients who had undergone UPPP or LUPP and most of whom presented with episodes of apnea during sleep (Lysdahl and Haraldsson 2002). Patients treated with UPPP were more severely symptomatic and had a higher average BMI before surgery. Symptoms associated with OSAS improved significantly in both groups, but UPPP was superior to LUPP in terms of most symptom parameters, including snoring. The authors concluded that LUPP was inferior to UPPP probably because of secondary narrowing of the retropalatal area following laser-induced scarring. However, the UPPP population presented preoperatively with tonsillar hypertrophy, and UPPP included tonsillectomy, whereas patients chosen for LUPP did not have any tonsillar hypertrophy or require tonsillectomy. This difference between the groups might also explain the tendency of poorer symptom improvement in the LUPP group. Hagert and colleagues evaluated snoring and daytime sleepiness with questionnaires during a follow-up period ranging from one to eight years after UPPP or LUPP (Hagert et al. 1999). Less snoring occurred in 90% and snoring disappeared totally in 18% of their study population, patients with OSAS or habitual snoring. The daytime sleepiness was disappeared in 25% of the study population. Symptoms improved more among all patients who had undergone UPPP but this tendency was not seen in patients with OSAS.

Levring-Jäghagen and colleagues studied patients treated with UPP without tonsillectomy for mild OSAS or snoring (Levring-Jäghagen et al. 1999). Only patients reporting persistent dysphagia one year after operation were examined further with videoradiography. 41% of these symptomatic patients had also objective findings, e.g., retention or dysmotility, but most of the dysphagic patients reported that the overall effect of UPP was beneficial and exceeded the deglutitional inconvenience. This study showed a similar appearance of dysphagia after UPP (29%) as reported earlier for LUPP (27%) operated patients (Isberg et al. 1998). The authors of this study concluded that patients intended for soft palatal surgery should be informed preoperatively about possible side-effects, e.g., dysphagia (Levring-Jäghagen et al. 1999). Another study by Levring-Jäghagen and colleagues also evaluated the incidence of dysphagia after various soft palate treatments (Levring-Jäghagen et al. 2004). In this study UPP patients were operated on with either laser or by blunt dissection and compared with patients having conventional UPPP. UPP and LUPP were performed under local anesthesia and UPPP under general anesthesia. In the case of UPP and LUPP the incision was made between the upper parts of the anterior pillars, and extended medially close to the lower margin of the soft palate where most of the uvula and its musculature were resected before suturing. There was no difference between these surgical modalities in terms of treatments response. Dysphagia was reported by 17% of the patients before surgery and by 29% after. Preoperative dysphagia was not associated with further deterioration after surgery, and the relief of snoring (93%) and daytime sleepiness (95%) outweighed the deglutition complaint.

For the treatment of OSA, LUPP carries no significant disadvantages compared to conventional UPPP. The pain level after LUPP should be lower than after UPPP, or

at most similar, as LUPP does not include tonsillectomy, as is the case for UPPP. The removal of the tonsils should be beneficial to the patient and favoured, if significant hypertrophy is present. LUPP in selected OSAS patients provides a good long-term result and remains an option for treatment of obstruction at the velopharyngeal level.

#### 2.9.1.3. Uvulopalatal flap

The uvulopalatal flap technique, a modification of UPPP, was presented as a treatment for snoring and OSAS patients by Powell and colleagues (Powell et al. 1996). This technique is a less invasive option to traditional UPPP, since it does not involve the uvulopalatal musculature which is saved. In the study of Hörmann and colleagues, there was a significant reduction of the average AHI (from 19 to 8/h) and the success rate of the uvulopalatal flap technique was 47% (Hörmann et al. 2001). The efficacy is similar to the original UPPP. Li and colleagues treated OSAS patients with the extended uvulopalatal flap technique and reported a mean AHI reduction from 42 to 13/h and a success rate of 82% (Li et al. 2003). In another study they reported that the success was 84% rate for the same surgical technique and that the technique led to an increase of the retropalatal space (Li et al. 2005). Overall, the literature on the isolated uvulopalatal flap is scant since this procedure is mainly used in multi-level surgery.

Friedman and colleagues compared UPPP including tonsillectomy with a palatal flap technique that involved tonsil reduction with radiofrequency coblation for treating OSAS patients (Friedman et al. 2004b). There was no statistical difference between the treatment groups as assessed with PSG on average 12 months after the operation. UPPP yielded a slightly weaker success rate than the uvulopalatal flap technique (55 vs. 70%). However, the group of UPPP was fraught with excessive morbidity, e.g., profound and prolonged pain and delayed recovery. Also risks for postoperative haemorrhage (18 vs. 0%), velopharyngeal insufficiency (9 vs. 0%) and dysphagia (18 vs. 10%) were higher among patients operated on with UPPP than those who were treated with the palatal flap.

Zetapharyngoplasty, which preserves the uvula, was initially introduced to treat snoring and sleep disorders. Mukai and Nitta demonstrated that the apnea index decreased after the operation from an average of 3 to 1/h (Mukai and Nitta 2002). Zetapalatopharyngoplasty (ZPP) was presented by Friedman and colleagues for enlarging the retropalatal space with a more aggressive technique than the uvulopalatal flap or UPPP (Friedman et al. 2004c). ZPP and uvula resection showed a higher cure rate (70%) of OSA than UPPP (30%), and both treatments were combined with tongue base surgery. A finding was similar in another study where ZPP was performed as secondary surgery to treat OSAS patients after failed UPPP (Friedman et al. 2007b).

#### 2.9.1.4. Laser-assisted uvulopalatoplasty

Kamami introduced laser-assisted uvulopalatoplasty (LAUP) for treatment of snoring (Kamami 1990). After the original article different techniques have been published and these have usually employed one to five sessions to complete the treatment. LAUP is a

modification of UPPP, but no suturing or tonsillectomy is performed. Kamami presented later a study on the use of LAUP for OSA and reported that 87% of the patients responded, as the RDI was reduced by more than 50% and as 44% of the subjects were cured with totally disappeared apneas (Kamami 1994). A variety of publications deals with LAUP for OSA, but the follow-up periods have been three to six months, and only rarely have the criteria of Sher been used or the AHI reported.

Still, trials lasting on average three months show a quite weak response of OSAS patients to LAUP; the average success rate was 36% counted in proportion according to four separate studies (Mickelson and Ahuja 1999, Walker et al. 1999, Ryan and Love 2000, Seemann et al. 2001). The response declined over six months or more of follow-up and the average success rate fell to only 17% and the average AHI increased in the whole population from 22 to 25/h (Berger et al. 2003, Ferguson et al. 2003). Larrosa and colleagues performed a placebo-controlled study and showed that there was no difference between LAUP and sham operated patients if the treatment effect was assessed in terms of AHI (Larrosa et al. 2004). Further, Finkelstein and colleagues reported that there was a tendency of increasing apnea after LAUP (Finkelstein et al. 2002). A UPPP-controlled evaluation involving radiocephalometric contrast examinations confirmed that the retropalatal obstruction did increase after LAUP, unlike UPPP (Finkelstein et al. 1997). This may be counteracted by the fact that a uniform practice in LAUP is to remove paramedian sector-like parts of the soft palate on both sides of the uvula rising to a height of 1-2 cm and thereafter to resect the uvula. In LAUP, the palatoglossal and palatopharyngeal musculature is penetrated. Such through-cutting surgery of soft palatal muscles may result in uncontrolled scarification and to an unpredictable healing process leading to retropharyngeal obstruction. According to Littner and colleagues, LAUP should be used, if necessary, only for the treatment of socially disturbing snoring and if it is used, sleep study evaluations should be performed to exclude OSA preoperatively and also postoperatively (Littner et al. 2001). Recently, the American Academy of Sleep Medicine no longer recommended LAUP for the treatment of SDB (Walker 2003, Aurora et al. 2010).

#### 2.9.1.5. Transpalatal advancement pharyngoplasty

Woodson and Toohill introduced transpalatal advancement pharyngoplasty (TAP) for surgical treatment of retropharyngeal obstruction (Woodson and Toohill 1993). They showed that TAP increased the retropalatal and oropharyngeal space after advancement of the soft palate by removal of the posterior border of the hard palates. Studies concerning TAP for OSA can be divided into two categories: first stage TAP and TAP following UPPP as a secondary operation (Woodson and Toohill 1993, Woodson 1997). The target population for TAP consists of OSAS patients with a narrow retropalatal airway lying superior to the point of palatal excision used in traditional UPPP. Anatomical deformation, a low palate, a large tongue in combination with small tonsils or secondary obstruction of the soft palate level caused by previous trauma or surgery of the upper airway may favour TAP. The success rate of first stage TAP in the study of Woodson and Toohill was

67%; at the same time the average AHI decreased with 77% (from 53 to 12/h) (Woodson and Toohill 1993). In another study of Woodson, plain UPPP was performed first and after tissue recovery a secondary TAP followed: the postoperative AHI decreased with 61% (from 75 to 29/h) and the success rate was 75% (Woodson 1997). The same study concluded that TAP increases the retropalatal area (321%) and decreases the collapsibility of the upper airway at the velopharyngeal and nasopharyngeal level in comparison to the results of UPPP performed earlier. Clearly, TAP is a procedure to be considered for more severe OSAS patients and for non-responders who have undergone UPPP or are not candidates for UPPP (Woodson and Toohill 1993, Woodson 1997, Woodson 1999, Woodson et al. 2005). TAP is a markedly more invasive procedure than UPPP and carries a risk of short-term complications, e.g., fistulas and uvulopalatal flap necrosis (Woodson and Toohill 1993).

#### 2.9.1.6. Palatal stiffening operation

The palatal stiffening operation assisted with laser was introduced by Ellis for the treatment of snoring due to palatal flutter (Ellis 1994). Mair and Day have showed that the cautery-assisted palatal stiffening operation (CAPSO) is effective against snoring, but there are only a few studies on its usefulness for the treatment of patients with OSAS (Mair and Day 2000). In a study of mild to moderate OSAS (inclusion criterion  $AHI > 10/h$ ) patients (BMI 29 kg/m<sup>2</sup>), Wassmuth and colleagues used electrocautery to dissect centrally off the mucosal flap of the soft palatal anterior surface, uvula included, but preserved the palatal muscles intact and open (Wassmuth et al. 2000). There was a 34% decrease in mean AHI (from 25 to 17/h) and a success rate of 40% (Sher's criteria with  $AHI < 10/h$ ) at three months of follow-up and stiffened tissues due to fibrosis healing. Pang and Terris evaluated a similar population (BMI 28 kg/m<sup>2</sup>) with mild OSAS ( $5 < AHI < 15/h$ ) undergoing CAPSO (Pang and Terris 2007). The mean AHI decreased with 58% (from 12 to 5/h) by three months postoperatively, but neither individual data nor success rates were presented.

Stiffening procedures are not recommended for mild OSAS since postoperative healing is prolonged and the patient experiences severe pain due to the mucosal defect. Further, there is limited experience and a lack of long-term follow-up results from palatal stiffening operations.

#### 2.9.1.7. Palatal implants and palatal injection therapy

In an attempt to introduce a less invasive form of treatment to decrease velopharyngeal narrowing in SDB, a palatal implant has been used first for snoring (Maurer et al. 2005). Palatal implants produce only minimal pain and cause minor partly reversible anatomical changes. Two randomized, double-blinded, placebo-controlled studies on the efficacy of palatal implants versus sham operation for patients with OSAS have reported decreased AHI values and a surgical success rate of 45% and 26% (Friedman et al. 2008, Steward et al. 2008). By choosing the AHI of  $< 20/h$  for succeed surgery instead of  $< 10/h$ , Friedman and colleagues were not precise in thinking that preoperative average AHI (23/h) was

already near to this limit of “success”. The average AHI decreased by 33% after three months of follow-up, but the average lowest SaO<sub>2</sub> after the operation was unchanged when compared to baseline or to the sham procedure. Steward and co-workers found that patients who were treated with implant had an increase in the AHI 17% (from 17 to 20/h) three months after operation, but this was, statistically significantly better than among patients who underwent sham procedure. In this study the Sher’s surgical success rate limit (AHI<20/h) was invalid when compared to the preoperative average AHI values.

Non-controlled trials on palatal implants have involved similar patients with preoperative AHI-values between 10 and 30/h and BMI<30-32 kg/m<sup>2</sup> as inclusion criteria. The success rates have ranged from 15 to 50% and the postoperative decrease in AHI from 12 to 27% but data on SaO<sub>2</sub> have not been presented (Nordgård et al. 2006, Walker et al. 2006, Goessler et al. 2007, Nordgård et al. 2007). The overall success rate counted in proportion from these four studies was 29%.

Palatal implants may be moderately effective as a treatment for mild OSA, but further studies to compare different treatments are needed. The long-term effects are not known, since the studies published thus far have presented a follow-up time of three months (in one study 12 months). Therefore, patients with mild OSAS may be suitable for treatment with palatal implants, if there is no need for expanding the hypopharyngeal space. These patients should preferably have snoring as their main complaint and have no other SDB related symptoms or co-morbidities associated with OSAS.

Injections of sclerosing agents are used to achieve scarring and stiffening of the soft palate to treat flaccid uvulopalatal regions and to relieve snoring (Brietzke and Mair 2001). The enthusiasm for this type of mini-invasive treatment for OSA has dwindled, since it requires repeated sclerotherapy injections, may be associated with transient palatal fistulas and is poorly documented in the literature.

#### 2.9.1.8. Radiofrequency ablation treatment of the soft palate

Powell and colleagues presented the technique of radiofrequency volumetric tissue reduction of the soft palate as a form of treatment of patients with SDB. They reported that snoring is reduced effectively two to three months after the procedure, once the palatal tissues have healed (Powell et al. 1998). By PSG, however, the procedure did not provide any clinically relevant effects. Radiofrequency (thermal) ablation, RFA (RFTA), of the soft palate and uvula region is mainly used to treat snoring, which is the main focus of most studies. There are only limited data on the efficacy of soft palate RFA in OSA. In two non-randomized studies with a short-term follow-up time, moderate improvement in terms of lowered AHI occurred when RFA treatment was repeated two to three times (Brown et al. 2001, Blumen et al. 2002). The mean AHI decreased with 48% (from 19 to 10/h) and the success rate was 66%, but the average lowest SaO<sub>2</sub> did not change among non-obese patients (BMI≤30 kg/m<sup>2</sup>) in the study of Blumen and co-workers. Although Brown and colleagues reported a mean AHI-reduction of 19% (from 31 to 25/h) in obese patients (BMI≤35 kg/m<sup>2</sup>) with moderate OSAS, their success rate was



only 17% and no other breathing parameters during sleep were improved. Pang and Siow reported in a non-randomized study that patients (mean BMI 23 kg/m<sup>2</sup>) with mild OSAS had a non-significant reduction of AHI (from 14 to 10/h) after RFA treatment of the soft palate (Pang and Siow 2009). Bassiouny and colleagues compared radiofrequency assisted uvulopalatoplasty and soft palate RFA in a randomized study among patients (BMI ≤ 30 kg/m<sup>2</sup>) with mild to moderate OSAS (AHI 10-30/h) (Bassiouny et al. 2007). The AHI decreased in the uvulopalatoplasty group with 53% (from 17 to 8/h) and RFA with 36% (from 15 to 10/h) at four months' follow-up. The success rate was 45% and 25%, respectively, as based on an AHI of less than 10/h and a reduction of at least of 50% from preoperative values.

According to these studies, there is no evidence that RFA treatment of the soft palate region is beneficial in mild to moderate OSA. This is supported by the study by Bäck and colleagues, who assessed the efficacy of RFA in the treatment of mild OSAS (AHI 5-15/h) of patients with a BMI < 35 kg/m<sup>2</sup> (Bäck et al. 2009). According to this randomized placebo-controlled study, neither AHI nor the symptoms of mild OSAS within either treatment group or between the treatment groups improved. Further, there were no differences between or within the two groups by cephalometric radiography.

RFA is not recommended as single-stage treatment of the soft palate for mild OSA. If heavy snoring is the primary indication, RFA may be used to treat SDB patients who do not need CPAP and do not have other symptoms than socially disturbing snoring. Among SDB patients it must be taken into consideration prior to RFA treatments of soft palate that possible other surgery of this region is performed in stiffened tissues due to ablation therapy.

#### 2.9.1.9. Tonsillectomy

Tonsillectomy with or without adenotomy of pharyngeal tonsils is an efficient procedure for OSAS if the patient has enormous adenoid hypertrophy. Two articles concerning young adults with OSAS have reported success rates ranging from 89 to 100% with the mean AHI reduction from 49 to 8/h (Houghton et al. 1997, Verse et al. 2000). Massive hypertrophy of the palatine adenoids is rare after childhood and adolescence, but if it occurs in patients, with a BMI less than 25 kg/m<sup>2</sup>, it may be treated with tonsillectomy alone (Nakata et al. 2006). Tonsillectomy should be performed if the palatine level is involved in causing obstruction and may be complemented with additional surgery. RFA to treat hypertrophy of the palatine tonsils of adults with OSAS has not been reported extensively as a single treatment. RFA performed tonsillectomy has not considerable advantage according to recent knowledge over traditional tonsillectomy for treating OSA excluding minimally invasive nature of RFA.

#### 2.9.2. Tongue base and hyoid surgery

Retrolingual obstruction is a common finding, especially in moderate to severe OSA, where it is usually accompanied with velopharyngeal narrowing. Two different

advancement strategies of surgery are available for OSA caused by retrolingual or hypopharyngeal obstruction. In case of hypertrophy of the lingual adenoid tissue at the base of the tongue or relative macroglossia in proportion to the pharyngeal cavity, reduction of the tongue volume may be appropriate. Flaccidity of connective tissue attaching the tongue to its surrounding, rigid and half-stable structures, and a loose tonus of the surrounding musculature and other nearby tissues may cause obstruction in certain sleep positions. Therefore it can be useful to reposition the adherent structures for some OSAS patients.

#### 2.9.2.1. Partial tongue base resection

Most of the studies concerning partial tongue base resection performed with laser assistance for OSAS patients are related to the time before RFA. The risk of obstructive edema and bleeding must be taken in consideration postoperatively especially if partial resection of the epiglottis has been performed in the same session. Fujita and colleagues reported first on the use of laser for partial tongue resection as single procedure to treat OSAS patients. They had a decrease in AHI (from 56 to 37/h) and a success rate of 42% (Fujita et al. 1991).

Partial tongue resection is rare procedure and studies are few. The reported success rate has varied between 79 and 25% (Woodson and Fujita 1992, Mickelson and Rosenthal 1997). Often tracheostomy is needed at the end of the procedure and this has, understandably, diminished the enthusiasm to use this procedure to treat OSA, especially since less invasive treatments are available.

#### 2.9.2.2. Radiofrequency ablation treatment of the tongue base

RFA saves the mucosal surface and is technically mini-invasive. These are the main benefits of RFA for treatment of obstruction at the tongue base level by reducing tissue volume without significant mutilation of the tissues. Powell and colleagues used RFA for tongue base to treat OSAS patients who had been incompletely treated with UPPP. They reported a 55% decrease in mean AHI (from 40 to 18/h) after RFA (Powell and colleagues 1999). The surgical success rates of RFA to treat tongue base obstruction in OSAS patients has varied between 20% and 63% in five reported studies (follow-up of 3 to 28 months) (Powell et al. 1999, Woodson et al. 2001, Stuck et al. 2002, Riley et al. 2003, Blumen et al. 2006). The success rate counted in proportion from these five studies all together is 32%, and the reduction in average AHI 32% (from 40 to 27/h). An average of 4.7 sessions of RFA treatment was given after individual healing intervals.

An adequate response treatment is thus achievable after several RFA sessions but requires long-term commitment of the patients. RFA allows treatment of retrolingual obstruction caused by macroglossy with limited trauma. The response among patients with a preoperative AHI 30/h or less may be better than if AHI is higher (Woodson et al. 2003). The mini-invasive nature of RFA method suggests that RFA could also be used to treat more severe OSAS patients, if there is a need to reduce the tongue base volume.

RFA may be used in combination with other surgical methods, as part of multi-level surgery in an all-in-one operation or in staged surgery.

#### 2.9.2.3. Tongue suspension

Originating from the glossopexy using a fascia lata, the Repose® System (Influ ENT, CA, USA) was first used to treat obstruction at the retrolingual level by DeRowe and colleagues who demonstrated a success rate of 29% in OSAS patients at two months follow-up (DeRowe et al. 2000). A similar success rate (29%) with the same suspension system has been published in another study covering two months of follow-up (Woodson 2001). A recent study by Hamans and co-workers reported a success rate of 67% among moderate OSAS patients with retrolingual obstruction who were treated with an adjustable tongue advancement technique consisting of a lingual tissue anchor and a tether line attached with a titration spool to the mandibula (Hamans et al. 2008). They used the Advance System® (Aspire Medical, CA, USA), and reported a 48% reduction in the AHI (from 23 to 12/h) over a follow-up time of six months. The main problem of tongue suspension techniques (Advance® and Repose® systems) is the risk of reduced retraction power created of the tongue due to loosening and re-modification of the soft tissues over time. Another possible drawback regarding suspension treatment is malfunction of the tongue during daytime, with a risk of changes in swallowing and speaking due to disturbances caused by tightened tissues and musculature.

#### 2.9.2.4. Hyoid suspension and hyoidthyroidpexia

Kaya presented sectioning of the hyoid bone as a therapy for OSAS patients with hypopharyngeal obstruction (Kaya 1984). Surgery of the hyoid level is based on the findings from radiological cephalometry studies showing an abnormal low position of the hyoid in OSAS patients in relation to the maxilla-mandibula and cervical vertebrae (Riley et al. 1985). Two techniques have been presented in the literature after the original report by Riley and colleagues (Riley et al. 1986): modified hyoid suspension (Riley et al. 1994) and hyoid suspension without suprahyoideal myotomy with preservation of the ligament stylohyoidea (Hörmann and Baisch 2004). The reported success rate for hyoid suspension has varied from 40 to 53% (Riley et al. 1994, den Herder et al. 2005, Stuck et al. 2005). The success rate counted in proportion from these three studies all together is 48%. Hyoid suspension is mainly used as part of multi-level concept treatments of retrolingual obstruction, possibly in combination with tongue base RFA, in severe OSAS patients.

### 2.9.3. Laryngeal surgery

In patients who have a relatively large epiglottis and an abnormally increased elasticity of the epiglottal cartilage nocturnal obstruction may proceed toward OSAS. This specific type of laryngomalacia, so-called floppy epiglottis, is manifested usually after a trauma or in aging males. The position of the epiglottis can be classified in four stages: the epiglottis touches the tongue (stage 0), is deflected dorsally less than 45 degree (stage

1), deflected 45-90 degree (stage 2) and deflected more than 90 degrees (stage 3). Stages 2 and 3 are pathological and imply floppy epiglottis (Catalfumo et al. 1998). Fiberoptic endoscopy performed in supine position reveals patients with floppy epiglottic position and among these patients surgery of epiglottis is the therapeutic treatment (Verse and Pirsig 1999). In part of laryngeal obstruction, nasal CPAP is the treatment of choice. Patients with OSAS who present a floppy epiglottis CPAP may narrow upper airway due to collapse of epiglottis and in these situations surgery is appropriate. Also in case of daytime problems of inhalation operative treatment should be performed. Among more common causes of laryngeal OSA are neurological vocal cord paralysis, vocal cord paralysis caused by other diseases and surgical complications. In case of floppy epiglottis, a partial laser-assisted resection of epiglottis can be performed in stages (Golz et al. 2000). In the study by Golz and colleagues AHI decreased (from 45 to 14/h) after partial resection of the epiglottis of OSAS patients with floppy epiglottis.

#### **2.9.4. Nasal surgery**

Nasal surgery for OSA focuses on symptoms caused by obstruction. The mainstay of diagnostics is nasal inspection combined with endoscopy and radiological and rhinological examinations. The main purpose of all nasal surgery is to optimize nasal breathing of rhinological symptomatic patients. Maintenance of breathing through normal upper airway during sleep requires that there is no hypopharyngeal obstruction. Hypopharyngeal obstruction may be due to posterior protrusion of the tongue and tongue base, as the mouth is opened and mandibula moves back (Meurice et al. 1996). Nasal septum reconstruction with or without rhinoplasty in combination with lower turbinate surgery is the most appropriate treatment. Still, the success rate of nasal surgery alone is below 20% when OSA is treated and there are no studies reporting statistically significant AHI-changes or improved oxygen saturation after surgery (Verse et al. 2002, Verse and Pirsig 2003).

Breathing through the mouth increases upper airway resistance during sleep compared to breathing through the nose (Fitzpatrick et al. 2003). The nasal cavity and its internal structures are subjected to the overall resistance of the upper airway. This is confirmed in a study where a tendency for a more patent nasal cavity was observed after operating with laser-assisted UPPP on patients with OSAS (Antila et al. 1997). Reduced retropalatal obstruction decreased the negative pressure, caused by inspiration against narrow airways, and further normalized both the nasal cavity and the nasopharyngeal pressure. This phenomenon was, according to acoustic rhinometry, a consequence of released congestion in the middle parts of the nasal cavity. Similar results have been presented according to which there is less nasal resistance after UPPP in OSAS patients (Welinder et al. 1997). Nasal congestion even in patients with allergic rhinitis may increase the risk of mild to moderate OSAS (Young et al. 1997).

These findings regarding the impact of narrowed upper airway as a cause for increasing respiratory resistance imply that it might be useful to correct significant obstruction

sites in the nasal cavities of OSAS patients. Nasal surgery prevents also a high negative intraluminal pressure centrally to operation level. Therefore, nasal surgery should be combined with other upper airway surgery, if nasal obstruction is present and especially if the patient is symptomatic. Further, nasal surgery is very important for reducing the pressure needed for successful CPAP treatment and for improving compliance with CPAP among OSAS patients with disturbed nocturnal nasal breathing (Friedman et al. 2000b, Powell et al. 2001, Chandrashekariah et al. 2008).

### **2.9.5. Tracheostomy**

Tracheostomy was initially introduced to treat patients with extreme apneas (Kuhlo et al. 1969). Later, it was used as a standard treatment for OSAS (Simmons 1979). Tracheostomy was the first effective treatment for OSAS patients, and currently it is used as a permanent treatment only of patients with most severe OSAS without compliance to CPAP. Very often these patients have a high BMI that predisposes to hypercapnic respiratory failure.

In a study by Guilleminault and colleagues 50 tracheostomized OSAS patients were followed for an average of 1.3 years (Guilleminault et al. 1981). They reported a success rate of 100% (AHI<5/h) and the prevalence of central apneas was reduced throughout the first postoperative year.

Ledereich and colleagues followed OSAS patients treated either tracheostomy or with other surgical procedures (Ledereich et al. 1995). According to their study, 30 tracheostomized patients had only an average of 3% of apneas by PSG at five years of follow-up, whereas in a control group that had not undergone tracheostomy 35% had apneas during sleep. In a study by Browaldh and colleagues ten obese (median BMI 36 kg/m<sup>2</sup>) male patients with OSAS were followed after elective tracheostomy (Browaldh et al. 2008). After six months of follow-up two patients were needed CPAP after decannulation to treat problems in sleeping. Eight patients were studied with arterial cannulation and their median arterial oxyhemoglobin desaturation index of 4% (ODI<sub>4</sub>) had decreased from 88% (range 60-126) to 4% (range 1-87), all patients had a mean value of more than 50/h before treatment. Tracheostomy passes all upper airways and there is evidence that obstructive apnea can be cured in the long-term with a permanent tracheostomy.

A retrospective follow-up study (average eight years) by Thatcher and Maisel found that the long-term use of a cannula through the tracheostoma eliminated OSAS in all of 79 obese (mean BMI 41 kg/m<sup>2</sup>) patients (Thatcher and Maisel 2003). The preoperative average AHI was high (81/h), but the authors did not report the postoperative AHI values and 16 subjects were decannulated for various reasons over the following years. The mortality rate was 2.5% during postoperative time. There was morbidity due to infections, local granulation tissue and scar formation. During the total follow-up time the authors reported another 12 deaths, none due to the tracheostomy: mortality followed the expected rate with regard to age and obesity. Partinen and co-workers studied a group

of patients with severe OSAS: 71 underwent tracheostomy and 127 were enrolled in a weight reduction group. They reported that mortality was increased in the latter group at five years of follow-up (0 vs. 14) (Partinen et al. 1988b). In another study, 385 male patients with OSAS were followed and those who were treated with tracheostomy did not present with any higher mortality than those with CPAP over a follow-up time of eight years (He et al. 1988). Thus, it seems that tracheostomy is highly effective in decreasing mortality in long-term and does not differ from CPAP in this sense.

Kim and colleagues reported a surgical cure rate of 74% (AHI<20/h) after tracheostomy in a series of 23 patients with OSAS: the mean AHI decreased from 58 to 20/h but the duration of follow-up was not reported (Kim et al. 1998). Some of their patients were non-responder due to cardiopulmonary decompensation and had central apnea. A similar recurrence of sleep apnea following tracheostomy was reported by Fletcher: obstructive apnea was decreased but changed in part to the central type of apnea in some of OSAS patients (Fletcher 1989). The possibility of central apneas and residual obstructive apneas must be considered and controlled for OSAS patients after any treatments.

The immediate postoperative risks after tracheostomy are haemorrhage, local cellulitis and infection in fascia level. The risk for developing postobstructive pulmonary edema must be considered in patients who are symptomatic after tracheostomy. Postobstructive pulmonary edema may occur in two thirds of the patients, but if present it is severe in less than 10% (Burke et al. 2001). The long-term adverse effects of tracheostomy after early stage problems, e.g., stoma granulation and closing tendency, are excessive mucotic secretion, respiratory tract colonisation, recurrent infections in the lower airways and mental problems (Conway et al. 1981, Guilleminault et al. 1981, Browaldh et al. 2008).

According to the recent literature tracheostomy is a highly effective treatment for severe OSAS patients. Tracheostomy allows long-term normal sleep and an AHI-value of less than 5/h and no devices disturbing the sleep are needed. There are problems related to tracheostomy that causes morbidity, with range from the cosmetic stigma to recurrent stenosis of the stoma. However, tracheostomy may be valuable form of treatment of patients who cannot use CPAP and who have OSAS accompanied by multiple cardiorespiratory diseases. Tracheostomy may be life-saving for patients with severe OSAS, if other surgical treatments are not feasible or possible due to poor general health.

## **2.9.6. Orthognathic treatment**

### **2.9.6.1. Oral appliances**

The recent interest in oral appliances has focused on mandibular advancement appliances (MAA), since only MAA has been documented efficacious in patients with OSAS in comparison to other devices which lift the soft palate (SPL) or retain the tongue (TRD). According to a review article MAA treatment is successful for patients with mild to moderate OSAS and the success rate has varied between 40 and 50% (Hoffstein 2007). However, the compliance rate for MAA lies between 56 and 68% after one to two years

from treatment start. Some of the patients who use the MAA are advised to undergo orthognathic surgery for long-term results, if they have problems using appliance or an inadequate response to MAA.

MAA has demonstrated better efficacy than UPPP. In a study by Wilhelmsson and colleagues, AHI decreased by at least 50% in 80% of the OSAS patients who used oral appliances, while rate was 60% in a control UPPP group (Wilhelmsson et al. 1999). AHI decreased by 50% or more in only 67% when the dropout rate in the MAA group was considered. Data from this particular study are not comparable with others, since the traditional Sher values were not reported as there was no criteria for a postoperative AHI-value under 10 or 20/h. Similar findings have been reported by Walker-Engström and co-workers in a study with a similar design (Walker-Engström et al. 2002). They showed a decrease in AHI of 50% or more in 81% of patients in the oral appliance group compared with 53% in the UPPP group after four years of follow-up. However, the long-term compliance with oral devices decreased to 62%, which reduced the overall success rate.

In a two-phased study by Hoekema and colleagues a group of OSAS patients were chosen to first use a protrusive mandibular repositioning appliance (Hoekema et al. 2006). A sleep study was performed while the protrusive device was in use, after which patients underwent surgery, the second phase of the study. After maxillo-mandibular advancement (MMA) surgery and a convalescence time of six months, the sleep study was repeated. Both treatments had a relatively high cure rate. MMA was clinically superior, as the preoperative AHI (50/h) decreased to 2/h; the corresponding figure in the MAA group was 12/h.

In the Cochrane database evaluation, Lim and co-workers compared oral appliances and upper airway surgery or oral appliances as a single treatment for patients with OSAS (Lim et al. 2009). They recommended oral appliance therapy for patients with symptomatic mild OSAS, in case of late intolerance or after refusal of CPAP treatment. The mandibular protrusion created by MAA not only stabilizes and enlarges both the oropharyngeal and hypopharyngeal airways, but also reduces possible nasopharyngeal obstruction. In this sense MAA could be regarded as a form of multi-level treatment (Lowe et al. 1995, Smith and Battagel 2004). In cases requiring further invasive treatments, e.g., MMA surgery, MAA is important as a non-invasive device for predicting the success of facial skeleton correction therapy. MAA, like CPAP, is a reversible form treatment.

#### 2.9.6.2. Mandibular osteotomy with genioglossus advancement

There are no studies reporting the AHI response to mandibular osteotomy (MO) as an isolated surgical method to treat patient with OSAS. The efficacy of MO has been evaluated only in terms of AHI when combined with other operative procedures of multi-level surgery.

### 2.9.6.3. Maxillo-mandibular advancement

Kuo and colleagues used maxillofacial surgery to correct the malposition of the maxilla and mandibula in OSAS patients (Kuo et al. 1979). A simultaneous mobilization technique of both maxillas and the mandibula was presented later (Turvey 1982). MMA consisted of transverse osteotomies of both maxillas in a Le Fort I osteotomy manner and bilateral sagittal split osteotomy of the mandibula. In maxillomandibular deficiency, MMA may be used as the primary treatment to correct anatomical obstruction. MMA may be used also if other surgical treatments have not been successful. Operating on OSAS patients without maxillomandibular deficiencies but presenting a narrowed posterior airway, e.g., in the presence of velopharyngeal and hypopharyngeal obstruction of the upper airway, is also considered as candidates for MMA (Hochban et al. 1997, Bettega et al. 2000). Rare patients with facial structural anomalies and OSAS are not suitable for MMA, and for these patients the distraction osteogenesis may be an option (McCarthy et al. 1992).

There are three studies involving OSAS patients that report a follow-up time of at least six months after MMA (Bettega et al. 2000, Li et al. 2000a, Goh and Lim 2003). The success rate counted in proportion from these three studies all together is 85% (AHI from 67 to 10/h). MMA provides a postoperative AHI (<5/h) comparable with CPAP and has a success rate of 97 to 100%, which is similar to the therapeutic effect of CPAP (Hochban et al. 1997, Prinsell 1999). Similar finding has been reported in a review article with decreased average AHI-value (from 64 to 10/h) and a success rate of 86% after MMA (Holty and Guilleminault 2010). In the meta-analysis of Holty and Guilleminault they concluded, that predictive findings of increased surgical success were greater degree of maxillary advancement, younger age and preoperatively lower weight and AHI value.

### 2.9.7. Multi-level surgery

The concept of multi-level surgery presupposes that at least two levels of the upper airways are involved in narrowing and creating multi-level obstruction during apnea. A multi-level procedure presented for first time for the treatment of patients with OSAS was a combination of UPPP, MMA, partial glossectomy and genioglossus advancement to septal reconstruction and partial turbinectomies (Waite et al. 1989). The term and concept of multi-level surgery was defined by Riley and colleagues, who presented OSAS patients who had been operated by UPPP, hyoid suspension and MO with genioglossus advancement (Riley et al. 1993). The success rate in their study was 60% and AHI decreased from 48 to 10/h. The overall success rate counted in proportion from multi-level surgery studies that have reported success rates of Sher is 65% (Eun et al. 2008, Lin et al. 2008, Van den Broek et al. 2008).

Minimally invasive multi-level surgery is based on RFA treatments administered in one or several sessions. There are four studies presenting the surgical success rates or individual AHI-values preoperatively and postoperatively. In these four studies patients with mild to moderate OSAS were given combined RFA treatment during several sessions to the base of the tongue and the soft palate level; in one study the palate tonsils



were treated as well (Fischer et al. 2003, Steward 2004, Stuck et al. 2004, Ceylan et al. 2009). The overall success rate counted in proportion from these four studies all together is 47% (AHI from 30 to 16/h) at an average follow-up time of six months. None of these studies reported severe problems, such as haemorrhage or severe infection. In light of these results, RFA turns out to be a less invasive procedure associated with only minor morbidity and complications (Stuck et al. 2003). RFA constitutes a good treatment modality for mild to moderate OSAS patients presenting with combined retrolingual and retropalatinal obstruction.

There are several multi-level surgery strategies, like the Mannheim concept (Verse et al. 2006), but the Stanford protocol is the most distinguished basis and most referred as staged concept surgery study in the literature (Riley et al. 1993). According to the Stanford protocol, UPPP (Mannheim: uvulopalatal flap) including possible tonsillectomy is performed for creating retropalatal airway dilatation. This is combined with surgery to expand the hypopharyngeal and oropharyngeal volume: MO with genioglossus advancement and hyoid suspension (Mannheim: tongue base RFA and hyoid suspension). According to the staged surgery concept of Stanford protocol, these previous procedures are followed in a second phase either by bilateral maxillar or maxillomandibular advancement, if the first phase treatments have been insufficient. The overall success rate counted in proportion from staged multi-level surgery studies presenting success rates of Sher all together is 73% - population counted as starting at the first stage, and if necessary, part of them continuing to the second stage (Riley et al. 1993, Lee et al. 1999, Bettega et al. 2000, Li et al. 2000b, Hendler et al. 2001). Separately analysed, success rate is 54% after first stage surgery and after second stage 86% among re-operated patients according to the same studies.

Multi-level surgery provides efficient treatment for patients with severe OSAS. On the other hand, these invasive treatments cause substantial morbidity and contain a risk of complications related to the separate surgical procedures performed of multi-level surgery.

### **3. AIMS OF THE STUDY**

Tracheostomy was chosen as a surgery that fully bypasses the obstructive upper airway. The hypothesis for this study was that permanent tracheostomy is beneficial for patients with severe OSAS.

The general aim of this study was to analyze the efficacy of soft palatal surgery in patients whose predominant nocturnal breathing abnormality was partial upper airway obstruction during sleep.

The hypothesis was that laser-assisted uvulopalatoplasty (LUPP) is an effective treatment of patients with partial upper airway obstruction during sleep, provided that there is an elongated soft palate with or without tonsil hypertrophy.

The specific aims of the study are the following:

- I To study obese patients retrospectively after permanent tracheostomy for severe OSAS and to assess the long-term efficacy in terms of symptom relief and SCSB findings, after surgical bypass of all possible upper airway obstructing sites.
- II To study the feasibility of the ultrasound scalpel as an instrument for UPPP compared to laser-assisted surgery to treat patients with partial upper airway obstruction during sleep or posture-dependent OSAS.
- III To study the efficacy of LUPP as a therapy for patients with partial upper airway obstruction during sleep diagnosed and followed with a SCSB and digital fluoroscopy based collapsibility estimation.
- IV To study the impact of obesity in patients with partial upper airway obstruction during sleep by studying their body fat distribution and the histopathological findings of uvulopalatal specimen.

## 4. SUBJECTS AND METHODS

### 4.1. Subjects

#### 4.1.1. Patients with obstructive sleep apnea syndrome (I)

The patients included in the study were referred to the Department of Otorhinolaryngology – Head and Neck Surgery at the Turku University Central Hospital because of OSAS. Seven patients (53.4±9.8 yrs, range 41-64 yrs), five men and two women, with permanent tracheostomy for severe OSAS as inclusion criteria were screened from patient records. This population was morbidly obese – their average BMI was 46±9.7 kg/m<sup>2</sup>. Six of the patients had a history of cardiopulmonary problems, such as chronic obstructive pulmonary disease (COPD), hypertension, asthma, coronary artery disease and congestive heart failure. Other significant medical conditions were epilepsy, hypothyreosis, diabetes mellitus, and alcoholism. Six patients had failed on CPAP treatment and one was treated with emergency tracheostomy without previous CPAP. Four out of seven patients were operated on under local anesthesia due to the risks of general anesthesia. Two patients were treated afterwards in an intensive care unit because of perioperative development of CO<sub>2</sub> narcosis. Patients were trained in tracheostomy maintenance during the postoperative days on the hospital ward and discharged after three to four days.

#### 4.1.2. Patients with obstructive sleep apnea syndrome or partial upper airway obstruction during sleep (II)

The patients included in the study were referred to the Department of Otorhinolaryngology – Head and Neck Surgery at the Turku University Central Hospital because of partial upper airway obstruction during sleep or posture-dependent OSAS with mild to moderate findings. The forty patients, 30 men and 10 women, presenting with partial upper airway obstruction during sleep or posture-dependent OSAS were enrolled into this study after preoperative assessment by the surgeon. The surgical exclusion criteria were: ASA (American Society of Anesthesiologists) class more than three, BMI≥31 kg/m<sup>2</sup>, severe OSAS (AHI>30/h), chronic alcohol abuse, untreated hypertension, epilepsy, asthma, allergy to non-steroidal anti-inflammatory drugs (NSAID) and age under 18 or over 60. Forty patients were randomized into two groups: twenty to undergo UPPP with an ultrasound scalpel and twenty with laser. Among all patients (mean age 43.5±10.4 yrs, range 20-60 yrs) the mean BMI was 25.3±2.8 kg/m<sup>2</sup>.

#### 4.1.3. Patients with partial upper airway obstruction during sleep (III-IV)

The patients included in study III were referred to the Department of Otorhinolaryngology – Head and Neck Surgery at the Turku University Central Hospital because of partial upper airway obstruction during sleep. The 27 patients (23 men and 4 women) with

snoring and daytime sleepiness were having partial upper airway obstruction during sleep and they were enrolled into the study. The main inclusion criterion was partial upper airway obstruction events (more than 50% of all breathing abnormalities) during sleep as assessed with SCSB recording. Preoperative exclusion criteria were BMI $\geq$ 40 kg/m<sup>2</sup>, macroglossy, retrognathia, significant tonsil hypertrophy and nasal obstruction. All patients chosen for LUPP had an elongated uvulopalatal region causing obstruction; some patients presented with edema in the same area. Among all patients (mean age 47.7 $\pm$ 8.1 yrs, range 29-63 yrs) the mean BMI was 28.2 $\pm$ 0.6 kg/m<sup>2</sup>.

The patients included in study IV were referred to the Department of Otorhinolaryngology – Head and Neck Surgery at the Turku University Central Hospital because of partial upper airway obstruction during sleep. The 16 male patients enrolled into the study (five were also included in study III) presented in a preoperative sleep study with partial upper airway obstruction and minor episodes of obstructive apnea. As inclusion criteria partial upper airway obstruction was the predominant (more than 50% of all breathing abnormalities) form of respiratory abnormalities in the sleep study. Preoperative exclusion criteria were BMI $\geq$ 35 kg/m<sup>2</sup>, macroglossy, retrognathia, significant tonsil hypertrophy and nasal obstruction. All patients included in the study and chosen for LUPP had an elongated uvulopalatal region with or without edema. The mean age was 52.1 $\pm$ 6.4 yrs, range 41-64 years and the mean BMI 28.2 $\pm$ 3.1 kg/m<sup>2</sup>.

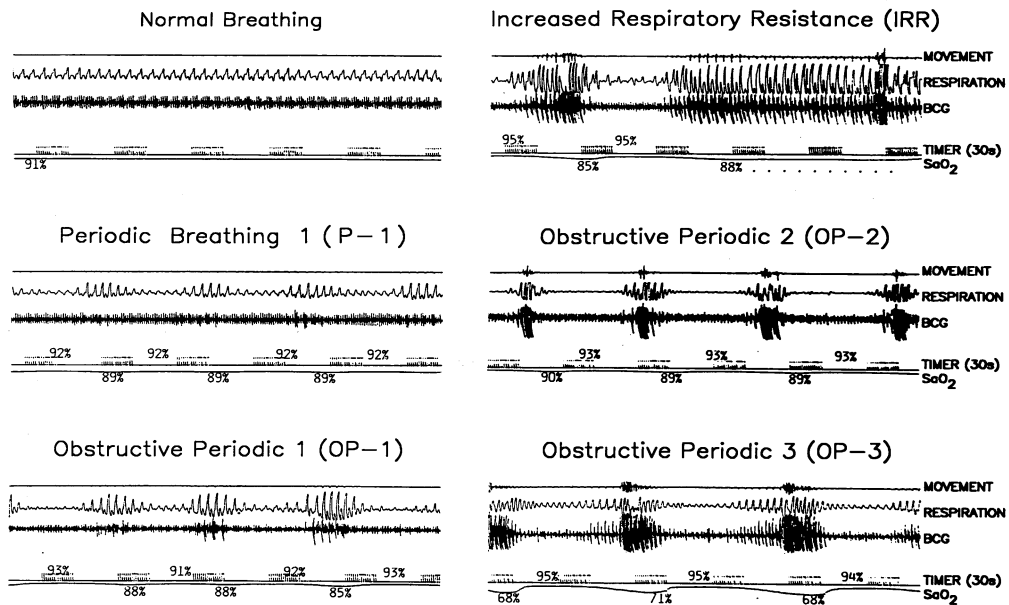
## **4.2. Methods**

### **4.2.1. SCSB recording (I-IV)**

The reason for choosing the SCSB (BioMatt<sup>®</sup>; Biorec, Turku, Finland) for respiratory monitoring during sleep was its unique capacity of distinguishing episodes of obstructive hypopnea or apnea as well as prolonged periods of IRR (Polo et al. 1988, Polo et al. 1992, Kirjavainen et al. 1996b). This method enables identification of patients with partial upper airway obstruction during sleep, when AHI may underestimate the obstruction (Anttalainen 2008).

The preoperative and postoperative SCSB recordings were visually analyzed by a senior physician specialized in disturbance analysis (Polo O in studies II-IV), who was not informed about treatment interventions or other findings. The recordings were scored in three minute epochs according to conventional criteria (Polo 1992). Simple periodic breathing without body movements or high-frequency respiratory spiking was scored as periodic breathing type-1 (P-1). The epoch was scored as obstructive periodic breathing type-1 (OP-1) if spiking was present, and OP-2 if body movements had occurred. Obstructive periodic breathing with spiking and movement was scored OP-3. The IRR pattern was defined as gradually increasing spike activity and increasing respiratory effort over a minimum period of one minute. The sum of the various periodic breathing patterns together with IRR was determined as all breathing abnormalities (ALL). An epoch was scored as a periodic movement (PMS or PLM) positive if a series of at least

four consecutive movements of typical duration and interval were present (Rauhala et al. 1996). The frequencies of each abnormal epoch were expressed as percentage of time in bed (% of TIB). P-1 and OP-1 are considered to be manifestations of partial upper airway obstruction during sleep in non-rapid eye movement (NREM) sleep stages 1-2 or rapid eye movement sleep (REM), whereas IRR represents partial upper airway obstruction during sleep in slow wave sleep (stages 3-4, NREM). OP-2 and OP-3 correspond to episodes of obstructive sleep hypopnea or apnea (Polo et al. 1988, Polo 1992). Examples of the various abnormal breathing patterns and normal breathing as recorded by the SCSB are shown in Figure 3.



**Figure 3.** Signals of body movements, respiratory movements and ballistocardiogram (BCG), followed by time intervals (30 seconds) and SaO<sub>2</sub>. Findings of normal breathing and obstructive periodic breathing during sleep can be detected with the SCSB (reprinted with permission from Polo 1992).

SCSB was recorded preoperatively and postoperatively during the first recovery week and follow-up (range 2.5 to 7 yrs) averages once annually in study I. In studies from II to IV, SCSB was recorded preoperatively and repeated in study III, on average, six months postoperatively.

#### 4.2.2. Arterial oxyhemoglobin saturation recording (I-IV)

SaO<sub>2</sub> was monitored simultaneously with the recording of SCSB. A pulse oximeter attached to the finger probe (study I: ear probe) was used for recording SaO<sub>2</sub> (Biox 11; The BOC Group Inc, Louisville, CO, USA). Respiratory events with desaturation of 4% or more were considered significant and ODI<sub>4</sub> was defined as the average number of

such desaturations per recording hour. The minimum ( $\text{SaO}_2\text{min}$ ) and mean ( $\text{SaO}_2\text{mean}$ ) saturation values of arterial oxyhemoglobin during the night were calculated.

### **4.2.3. Surgical techniques**

#### 4.2.3.1. Tracheostomy (I)

Tracheostomy was performed under local anaesthesia with the traditional instrumentation of a scalpel, scissors and blunt dissection. All except one patient underwent tracheostomy electively; the one patient needed emergency tracheostomy due to severe respiratory problems.

#### 4.2.3.2. Laser-assisted surgery (II-IV)

LUPPP (II) and LUPP (III and IV) were performed with an infrared-diode laser using a wave length of light of 810 nm and 20 W, and an OPC-B015 (OptoPower corp., Tuscon, USA) contact fiber with an air cooling system and secondary suction for vaporized tissue gases.

Before operation the skin area of face was covered with gauzes moistened with saline water and if the patient was under general anesthesia (II) extra gauze was placed in the lower part of the hypopharynx, as well. Lidocain 40mg/ml cum epinephrine 10-15ml (II-IV) was injected in the uvulopalatal and paratonsillar regions after marking the anterior palatal resection line.

LUPPP was carried out according to the method of Fujita with minor modifications including ultrasound scalpel or laser-assistance (Fujita 1993). The tonsils were first removed together with minor resection of the palatoglossal and palatopharyngeal arches. A palatal mucosal incision was made along the line of the crease created by lifting the uvula gently upward, approximately 4-5 mm above the most superior point of palatoglossal arch. The veli palatini muscles located in the upper and medial region of the soft palate were preserved together with the posterior components of the palatoglossal muscles on both sides. After cutting through the lowest part of the anterior palatoglossal muscles and the uvular muscle, a posterior mucosal incision was made slightly lower than the anterior one and these two margins were then detached with four to five stitches without tension resulting in an intact mucosa facing the nasopharynx to prevent possible posterior stenosis.

LUPP was performed with a similar technique but not involving the posterior pillars of the tonsil cavity, which preserved the palatopharyngeal arch and its palatopharyngeal muscles intact. The tonsils, if present, were removed. Further, the palatoglossal arch was preserved in its medial margin as widely as possible to enable tension-free suturing of the superior part of the tonsil cavity and in the soft palate area. Finally, the superior part of the palatopharyngeal muscles together with the palatoglossal muscles were then detached with four to five stitches.

If there was visible tension around the superolateral compartment of the tonsil cavity at this point of the operation, a horizontal incision through the posterior pillar, i.e. the palatopharyngeal muscle, was made under the lowest suture in line to release posterior tension.

If a tonsillectomy had been performed previously, the surgical procedure was otherwise identical to what has been described above, with the addition that the mucosa with any underlying scar tissue from the upper third of the tonsil cavity was revised. After removal of this scar tissue both the palatoglossal and the palatopharyngeal muscles were exposed separately and the operation was followed by either LUPPP or LUPP.

#### 4.2.3.3. Ultrasound scalpel surgery (II)

UPPP (as described in 4.2.3.2.) with an ultrasound scalpel was performed with a 5 mm long sickle-shaped metal blade vibrating at a frequency of 55500 Hz (Harmonic Lancet, UltraCision Inc., Smithfield, RI, USA).

### **4.2.4. Histological analysis**

#### 4.2.4.1. Histological coagulation depth (II)

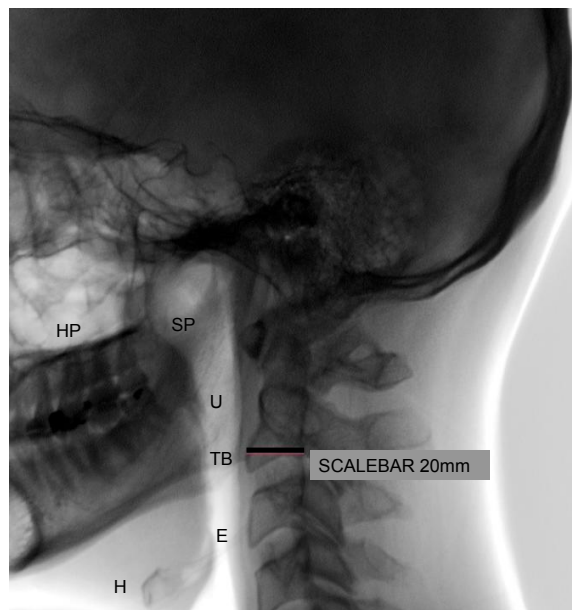
The resection block of the soft palate plus the uvula was collected for analysis of the histological depth of injury (mm) represented as coagulation. The resection block was placed in 4% phosphate buffered formaldehyde fixative immediately after removal. The specimen was sectioned coronally through the uvula and embedded in paraffin. One symmetrically cut representative microscopic section opposite to the middle part of the uvula was chosen for assessment of injury. Sections were stained with the Weigert-van Gieson method (“non-bleaching van Gieson”) (Van Gieson 1889, Weigert 1904). The histologist was blinded to any other clinical data.

#### 4.2.4.2. Histological tissue morphology (IV)

The resection block of the soft palate plus the uvula was placed in 4% phosphate buffered formaldehyde fixative immediately after removal. After fixation, the specimen was sliced coronally through the uvula and embedded in paraffin. One symmetrically cut representative microscopic section stained with Herovici (“non-bleaching van Gieson”) was selected for morphometric point counting (Herovici 1963). The whole field of the specimen was analysed under x 100 magnification. The tissue at each of the intersecting points was classified into one of the following categories: compact connective tissue, loose connective tissue, glandular tissue, muscle, fat, lymphatic tissue and vessel. The histologist was blinded to any other clinical data. The percentage of each tissue component was calculated  $[(\text{total number of points} - \text{points of other components}) / \text{total number of points} \times 100 (\%)]$ .

#### 4.2.5. Estimation of collapsibility in upper airway with digital fluoroscopy (III)

Digital fluoroscopy was performed approximately two weeks before LUPP. The patients were awake in supine position during the procedure, which was repeated on average six to seven months after surgery. The two images showing the minimum and maximum anteroposterior airway dimensions (AD<sub>min</sub> and AD<sub>max</sub>) were visually selected, and AD<sub>min</sub>/VP and AD<sub>max</sub>/VP were measured at the narrowest part of the velopharynx. The velopharyngeal narrowing was always immediately above the lower tip of the uvula. The oropharyngeal measurements (AD<sub>min</sub>/OP and AD<sub>max</sub>/OP) were made at the narrowest part of the oropharynx between the lower tip of uvula and the upper tip of epiglottis, whereas the hyoid measurement (AD<sub>min</sub>/H and AD<sub>max</sub>/H) was placed beneath the previous one at the hyoid bone. Due to the synchronous movement of the upper airway, AD<sub>min</sub> and AD<sub>max</sub> at each anatomical level were measured from the same imaging film (Figure 4 and 5). A subtraction technique was used to ensure that there was no head movement during imaging and also to help determine the AD<sub>max</sub> and AD<sub>min</sub> images. Collapsibility was defined as a dynamic change of the upper airway dimension over the breathing cycle and calculated as  $[(AD_{max} - AD_{min})/AD_{max}] \times 100$  (%) at the velopharynx, oropharynx and hyoid bone (Col/VP, Col/OP and Col/H) (Tsushima et al. 1996, Tsushima et al. 1997).



**Figure 4.** A single digital fluoroscopic image presented (6.3/s). The image has been rotated counter clockwise from the supine registration plain. Anatomic anterior borders lining the upper airway: hard palate (HP), soft palate (SP), uvula (U), tongue base (TB), epiglottis (E) and hyoid bone (H). Scale bar positioned at the caudal border of 2<sup>nd</sup> cervical vertebral body.

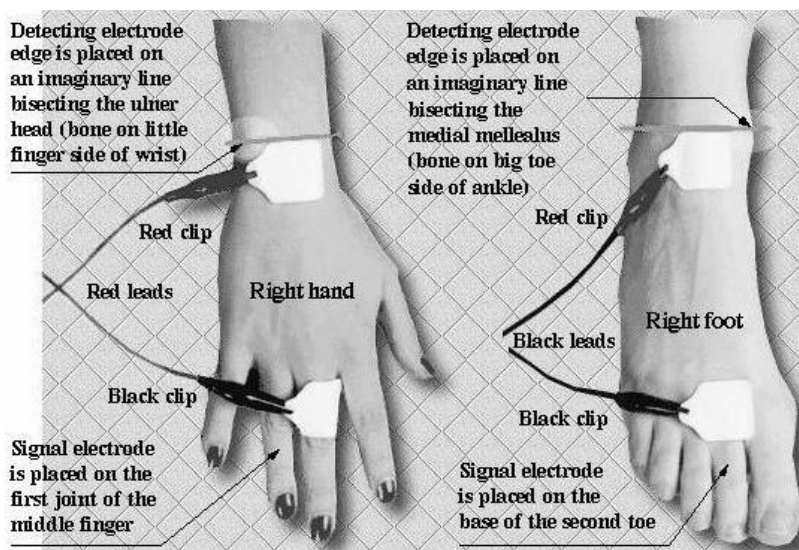




**Figure 5.** A single digital fluoroscopic image presented (6.3/s). The image has been rotated counter clockwise from the supine registration plain. Note change in upper airway during inspirium: there is a narrowing from the level of the soft palate to the tongue base and decreased hypopharyngeal patency.

#### 4.2.6. Body fat distribution (IV)

Body fat content and distribution were assessed by the BMI, the waist/hip-ratio (W/H-ratio), the skinfolds and by bioelectrical impedance analysis (BIA). Weight was measured at an accuracy of 0.5 kg and height of 0.5 cm. The W/H-ratio was based on waist and hip measurements at accuracy of 0.5 cm. Skinfolds were measured at an accuracy of 0.1 mm at the triceps, biceps, and subscapular and suprailiac skinfolds on the right side of the body with a skinfold caliper (John Bull Indicators LTD, UK). The body density was determined from the sum of these four skinfolds using the formula developed by Durnin and Womersley (Durnin and Womersley 1974). The body fat percentage was calculated using the equation described of Siri (Siri 1961). Hoffer and colleagues have presented the correlation of whole body impedance with total body water volume (Hoffer et al. 1969). This finding was further developed to assess the fat free mass of patients' body with bioelectrical impedance measurements (Lukaski et al. 1985). According to several studies BIA is valid approach for the estimation of human body composition. In present study impedance was measured with BIA-101A/S (RJL Systems inc., MI, USA). Patients were instructed to lie down with their limbs abducted. Two signal electrodes and two detector electrodes were placed on the dorsal surfaces of the right hand and foot (Figure 6). The validation of lean body mass estimation by BIA is described by Segal and co-workers, and their formula was used in this study to obtain the body fat percentage (Segal et al. 1988). The same person underwent all measurements three times. The average of the three measurements was used for the analyses.



**Figure 6.** Bioelectrical impedance estimation using electrodes placed on the hand and foot. Reprinted with permission from RJL Systems inc., MI, USA.

#### 4.2.7. Questionnaires (I-III)

##### 4.2.7.1. Questionnaire (I)

For assessment of the long-term effects of surgery, patients were asked to fill in a questionnaire at follow-up (range 2-7 yrs). Questionnaires were asked on the patients' general health, depression and symptoms associated with sleep disturbances. The questionnaires used in this study were unvalidated and formulated only for this study. Patients were requested to compare their sleep-related symptoms together with their general health and depression before and after follow-up and to give a value whether a specific symptom occurred after tracheostomy much more=1, more=2, similarly=3, less=4, or much less=5 often. The comparison of the occurrence of sleep-related symptoms before and after tracheostomy was made by patients on a scale from 1 to 5 (1=deterioration and 5=improvement). Finally, the patients gave their subjective opinion about the necessity of permanent tracheostomy as a long-term treatment for OSAS.

##### 4.2.7.2. Questionnaire (II)

Patients were asked to fill in a follow-up form. The questionnaires were unvalidated and formulated only for this study. The questionnaires reported several parameters, including pain, analgesic use, dietary intake and bleeding events.

Previous studies using a similar operative procedure have analyzed pain on a visual analogue scale (VAS) during convalescence (Hendolin et al. 1994, Virtaniemi et al. 1999, Troell et al. 2000, Nikanne et al. 2003). In this study, mild and insignificant pain

was defined as VAS 30 mm and less (Rawal 1999, Svensk förening för anestesi och intensivvård 2005). The same value for mild pain has been used in clinical practice and other studies (Hendolin et al. 1994, Virtaniemi et al. 1999, Troell et al. 2000). Primarily, VAS has been used in chronic pain assessment (Huskisson 1974, Scott and Huskisson 1976, Huskisson 1983).

VAS has also been adequate for measuring postoperative pain during the immediate follow-up period (DeLoach et al. 1998). Statistical tests comparing VAS for pain have demonstrated that it is reliable for detecting differences among groups (Dexter and Chestnut 1995). In the adult population VAS is sensitive to changes in pain levels or following instructions of pain medication during the postoperative time (Tyler et al. 1993, Rømsing et al. 1996).

The intensity of postoperative pain was assessed at 9.00 a.m., 3.00 p.m. and 9.00 p.m. every day for a period of ten days (day of surgery and ten postoperative days) using a 100 mm VAS. The use of analgesics was followed at the same intervals throughout the study period. In all operated patients pain medication consisted of a suppository of naproxen 500 mg (Pronaxen<sup>®</sup>, Orion Pharma, Finland), to be taken when needed, up to three times a day. Rescue pain medication consisted of a combination of paracetamol 500 mg and codeine 30 mg (Panacod<sup>®</sup>, Sanofi-Aventis, France), which was allowed up to eight times a day. Together with recording the frequency of various pain medications taken (number of drugs used) patients were requested to note any haemorrhage (+/-) and their ability to eat and to drink (1=none, 2=moderately, or 3=sufficiently) at the same intervals. All postoperative haemorrhagic events were reported in the follow-up forms. Postoperative bleeding was marked as positive on any particular day if a patient recorded one or more haemorrhagic events on the same day and negative if none.

An acceptable level of average maximum pain tolerated by the patients was evaluated preoperatively during the morning of the operation day on the VAS scale (0-100 mm), as each patient gave an estimation of the maximal postoperative pain he or she was ready to tolerate despite pain medication. This maximum pain level was used as the threshold of moderate or severe intolerable pain, whereas values of VAS exceeding 30 mm were considered to indicate insufficient pain medication. Any information about side-effects and the patient's personal opinion of the adequacy of pain medication at the end of the follow-up period (sufficient / insufficient) were also recorded.

#### 4.2.7.3. Questionnaire (III)

Patients were requested to assess their overall improvement in snoring and daytime tiredness using a 100 mm VAS. A value of 0 mm characterized unchanged and 100 mm totally disappeared symptom. The questionnaire used was unvalidated and formulated only for this study.

#### **4.2.8. Statistical analyses (II-IV)**

##### 4.2.8.1. Statistics (II)

The normality of continuous variables was tested by the Kolmogorov-Smirnov normality test. The mean differences of the values of the continuous variables between groups were compared with a two-sample t-test. The Mann-Whitney U-test was used for non-normally distributed continuous variables. The differences in sex distribution, postoperative side effects and adequacy of pain medication between the groups were tested with the Chi-square or Fisher's exact test. Pain medication as well as postoperative diet, drinking or eating, and bleeding events between the groups on each day were compared with the Mann-Whitney rank sum test. VAS-values of pain were analyzed with two-way repeated measures analysis of variance (ANOVA) and changes between each day with a paired t-test. A p-value of less than <0.05 was considered statistically significant. Statistical analyses were performed with SigmaStat 3.0 for Windows (Systat Software Inc., CA, USA).

##### 4.2.8.2. Statistics (III)

The Wilcoxon signed rank test was used to analyze the difference before and after LUPP. The interdependency of two variables was tested by Pearson correlation. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed with SigmaStat 3.0 for Windows (Systat Software Inc., CA, USA).

##### 4.2.8.3. Statistics (IV)

Statistical analyses were made using Pearson moment correlation product and p-value of less than 0.05 was considered statistically significant.

#### **4.2.9. Ethical considerations**

The patients in this study were operated on for OSAS and partial upper airway obstruction during sleep. All patients included in studies II, III and IV had the opportunity to obtain the relevant information regarding the operation, either UPPP or UPP, before consenting. All patients gave their informed consent to the study protocol, which was approved by the Ethics Committee of the Turku University Central Hospital. Patients in study I had been tracheostomized before consenting for clinical indications. All operations followed the standard surgical techniques of our clinic. In study III digital fluoroscopy was performed and this exposed the patients to a relative small radiation dose (1mSv), which was approximately one-fifth of the natural background radiation of one year in Finland (5mSv) (Crawley et al. 2004).

## 5. RESULTS

### 5.1. Tracheostomy for patients with severe obstructive sleep apnea syndrome (I)

#### 5.1.1. SCSB and arterial oxyhemoglobin saturation findings

SaO<sub>2</sub>min increased after surgery (p=0.002, follow-up time 5.1±2.6 yrs, range 2.5-9 yrs). Patient number seven showed only a modest increase of SaO<sub>2</sub>min and died of COPD 2.5 years postoperatively. Patient number two had morbid obesity (BMI 62 kg/m<sup>2</sup>) and presented with episodes of central apnea on SCSB despite tracheostomy. All patients responded with decreased frequency of obstructive sleep apnea episodes during sleep (Table 4). There was a clinically small but statistically significant decrease of BMI during the follow-up (from 46.0 to 42.7 kg/m<sup>2</sup>, p=0.036).

**Table 4.** Long-term follow-up results of permanent tracheostomy in patients with severe OSAS. SaO<sub>2</sub>min, SaO<sub>2</sub>mean and ODI<sub>4</sub> presented as % of TIB together with SCSB findings separating obstructive and central apnea. Median, mean and standard deviation (ST DEV) values are presented.

PATIENT No.	PREOPERATIVE			POSTOPERATIVE				ODI <sub>4</sub> % of TIB	FOLLOW-UP years
	SaO <sub>2</sub> min %	Obstructive Apnea	Central Apnea	SaO <sub>2</sub> min %	SaO <sub>2</sub> mean %	Obstructive Apnea	Central Apnea		
1	65	+	+	80	90.8	-	-	15	7
2	50	+	-	73	83.7	-	+	49	3
3	50	+	-	85	89.9	-	-	8	4
4	50	+	-	90	96.0	-	-	2	7
5	30	+	-	79	86.3	-	-	3	9
6	69	+	-	88	95.0	-	-	2	3
7	80	+	-	85	92.0	-	-	21	2.5
MEDIAN	50			85	90.8			8	4
MEAN	56.3			82.9	90.5			14.3	5.1
ST DEV	16.4			5.9	4.4			16.9	2.6

#### 5.1.2. Sleep-related symptoms, general health and depression

The individual quality of life of OSAS patients treated with tracheostomy was evaluated by scoring symptoms associated with sleep apnea by three different questionnaires. First, six patients were requested to compare sleep-related symptoms together with general health and depression before and after follow-up (Table 5). Four out of six patients (nr 1, 3, 5 and 6) reported marked improvement in the symptoms associated with sleep apnea. The symptoms of one patient (nr 4) were initially reversed but subsequently the general health was affected by depression and concomitant carcinomas. Another patient (nr 2)

who had a postoperative BMI increase with appearance of other diseases had symptom score three. The patients' general health, occurrence of sleep-related symptoms and sleep quality were improved after tracheostomy in this study population.

**Table 5.** Long-term follow-up results of permanent tracheostomy in patients with severe OSAS. Comparison of the occurrence of sleep-related symptoms before and after tracheostomy on a scale from 1 to 5 (much more=1, more=2, similar=3, less=4, or much less=5). Mean, standard deviation (ST DEV) and median values are presented.

Symptoms	Patients						Mean	Median
	1	2	3	4	5	6		
General health	4	4	5	1	4	4	3.7	4
Sleep quality	3	3	3	4	4	4	3.5	3.5
Depression	1	3	3	1	4	5	2.8	3
Daytime tiredness	4	2	4	2	4	4	3.3	4
Daytime sleep	4	3	4	2	5	-	3.6	4
Difficulties in falling sleep	4	3	5	2	5	4	3.8	4
Waking during the night	3	2	5	3	4	4	3.5	3.5
Apneas during the night	2	3	4	2	4	4	3.2	3.5
Nocturnal sweating	5	3	4	3	4	5	4.0	4
Snoring	5	5	4	5	5	4	4.7	5
Unrefreshing sleep	3	2	5	2	4	4	3.3	3.5
Morning headache	5	3	4	2	5	4	3.8	4
MEAN	3.6	3.0	4.2	2.4	4.3	4.2	3.6	-
ST DEV	1.2	0.9	0.7	1.2	0.5	0.4	0.5	-
MEDIAN	4	3	4	2	4	4	-	4

### 5.1.3. Outcome of tracheostomy

Six patients were requested further to self-analyse the occurrence of their current sleep apnea-associated symptoms and their quality of life. Only three (nr 1, 3 and 5) out of six patients reported a good or very good current quality of life. Two patients (nr 4 and 6) considered that tracheostomy had had a slightly positive and one (nr 2) a slightly negative impact on their quality of life.

All seven patients estimated possible problems caused by the tracheostomy. Three patients (nr 1 to 3) reported granulation tissue formation and secondary obstruction of the stoma. Other adverse effects mentioned by the patients included transient respiratory infections (nr 1 to 4 and 6) and excessive mucous secretion. None complained of social convenience due to the tracheostomy. All patients were able to speak normally and none required closure of the stoma. Regardless of some problems, all patients reported that the tracheostomy was absolutely necessary. Two patients suggested that a preoperative meeting with tracheostomized patients would have helped them to accept the intervention better.

## 5.2. Evaluation of ultrasound scalpel in UPPP (II)

### 5.2.1. Ultrasound scalpel for UPPP - comparison with laser-assistance

The ultrasound scalpel-performed UPPP group did not differ from laser-assisted surgery group in sex ( $p=0.715$ ), age ( $p=0.456$ ), BMI ( $p=0.114$ ), duration in the operating room or the operating time (Table 6). The degree of haemostasis during surgery and tissue injury of coagulation depth in histological specimens was not statistically significantly different between the groups. However, there was a 0.05 mm deeper (non-significant) coagulation injury with ultrasound scalpel. The cumulative data during first ten days after UPPP showed that patients who were operated on with the ultrasound scalpel had significantly less postoperative days of bleeding. One patient in the ultrasound scalpel group and three patients in the laser-assisted group required postoperatively further treatment of haemorrhage and were coagulated electronically under local anaesthesia as outpatients. No blood transfusions were given to patients during or after the operation in the follow-up time.

**Table 6.** Laser-assisted and ultrasound scalpel-performed UPPP. Average perioperative values are the operating time of UPPP (minutes), the total time in operating room (minutes) and the amount of blood collected from operative area (milliliters). Postoperative values are the average depth of histological coagulation injury (millimeters) and the total amount of bleeding positive days among all patients in each group (a day was reported as a bleeding day if any blood was observed by patients during ten-day follow-up). Corresponding p-values are presented.

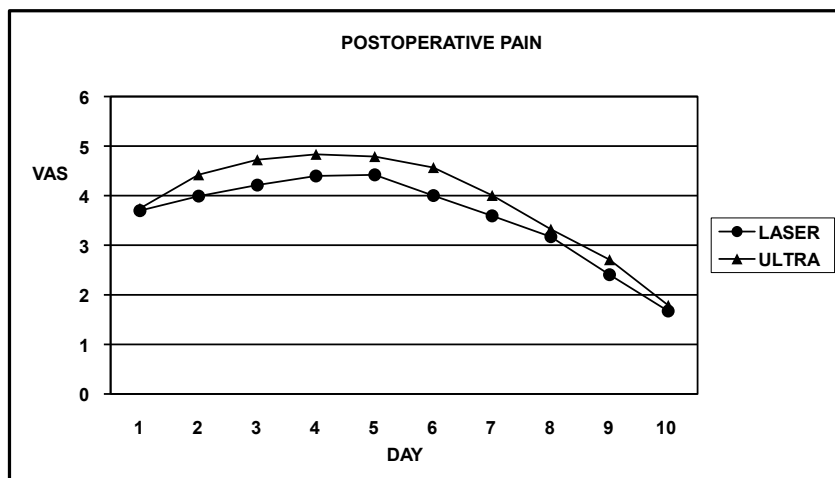
		LASER	ULTRA	p
<b>PERIOPERATIVE</b>	UPPP-TIME (min)	25 ± 5	24 ± 8	0.559
	OPERATING ROOM TIME (min)	59 ± 11	53 ± 11	0.105
	BLOOD (ml)	68	81	0.903
<b>POSTOPERATIVE</b>	COAGULATION (mm)	0.903	0.954	0.728
	DAYS OF BLEEDING (n)	33	10	0.037

### 5.2.2. Daily pain and pain medication after UPPP with laser-assistance or ultrasound scalpel

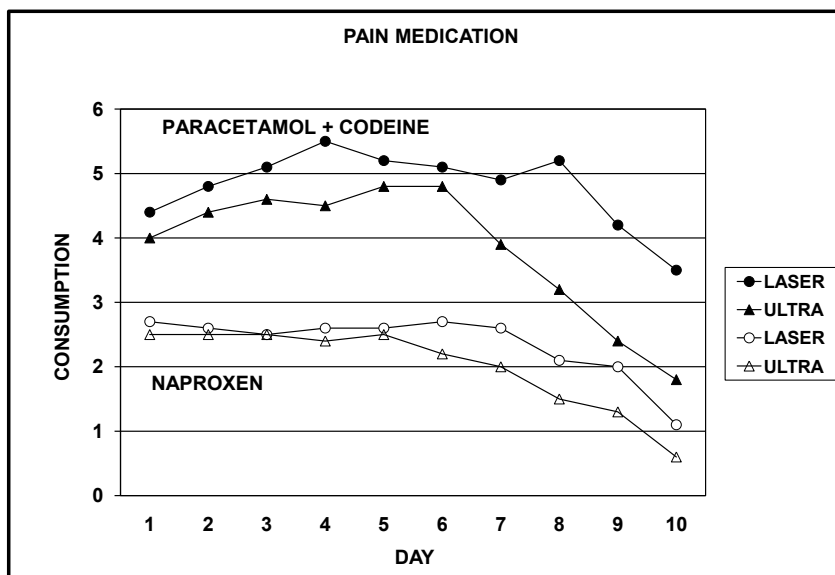
The VAS-values for pain were compared between the laser-assisted and ultrasound scalpel UPPP groups for 10-days. There was no difference ( $p=0.615$ ) (Figure 7). No difference was found either when comparison of VAS-values of pain was made between single days ( $p=0.991$ ) or at three time points of the day: 9.00 a.m. ( $p=0.775$ ), 3.00 p.m. ( $p=0.774$ ) and 9.00 p.m. ( $p=0.875$ ).

Every fifth patient reported from insufficient analgesia, but there was no difference in this respect between the groups ( $p=0.443$ ). The incidence of side-effects in patients using paracetamol-codeine combination (Panacod<sup>®</sup>, Sanofi-Aventis, France) and naproxen (Pronaxen<sup>®</sup>, Orion Pharma, Finland) was 18/40 (45%). The side-effects consisted mainly of fatigue, constipation, nausea, gastralgia and dizziness. The consumption

of paracetamol-codeine combination was higher throughout the entire recovery time among the laser-operated patients that the patients who had been operated on with the ultrasound scalpel (Figure 8).



**Figure 7.** Postoperative average VAS values (0-10) of pain from the day 1 to day 10 after laser-assisted and ultrasound scalpel-performed UPPP.

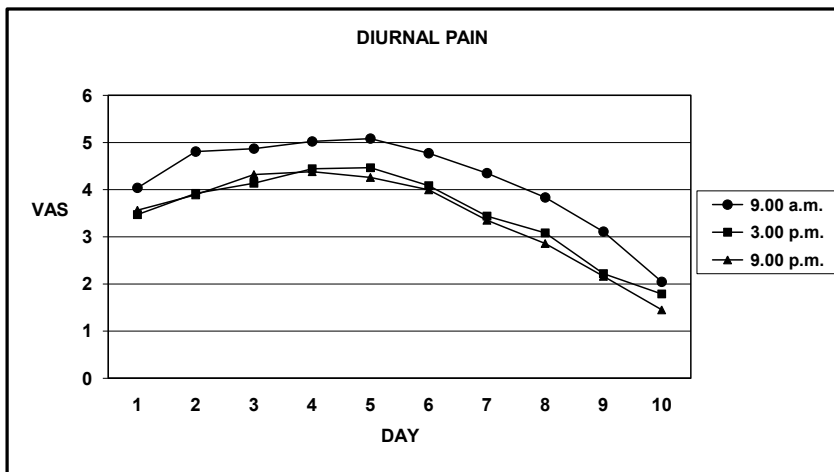


**Figure 8.** Postoperative consumption of pain medications from the day 1 to day 10 after laser-assisted and ultrasound scalpel-performed UPPP. During days 8 ( $p=0.027$ ) and 9 ( $p=0.037$ ) on the consumption of paracetamol-codeine was higher in the laser-assisted than the ultrasound operated group of patients.



### 5.2.3. Daily and diurnal pain variation after UPPP

The pain values were analyzed in the total population (n=40) of UPPP operated patients (both laser and ultrasound scalpel methods). The pain values increased each day during the first five postoperative days compared to day 1. From day 6 onward the pain values decreased and from day 8 onward there was less pain than on the first postoperative day. Compared to day 1 there was a significant reduction in pain on day 9 ( $p=0.002$ ) and day 10 ( $p<0.001$ ). This finding of decreased pain level was parallel to the finding of mild pain ( $VAS\leq 30$  mm) during days 9 and 10. Patients had significantly less pain at 3.00 p.m. ( $p<0.0001$ ) and at 9.00 p.m. ( $p<0.0001$ ) than at 9.00 a.m. during the entire length of the recovery time (Figure 9).



**Figure 9.** Postoperative average VAS values (0-10) of pain represented at the 9.00 a.m., 3.00 p.m. and 9.00 p.m. from day 1 to day 10 in the total population of 40 patients.

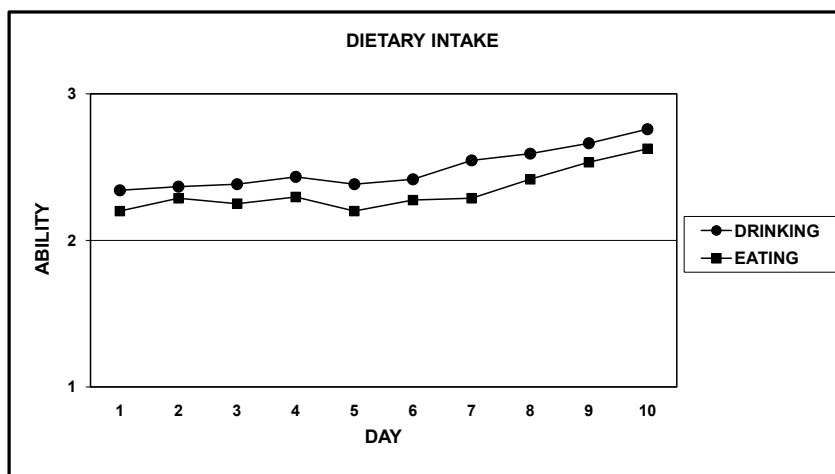
The patients' pain values were further analysed and compared to their subjective pain sensation. An acceptable level of maximum pain tolerated by each patient was evaluated preoperatively by VAS (0-100 mm) questionnaire. There was no significant difference in pain tolerance found between the ultrasound scalpel-performed and laser-operated groups ( $p=0.828$ ). The VAS data showed that VAS of 56 mm was the threshold between moderate and severe, intolerable pain. The distribution of VAS-values exceeding mild ( $VAS>30$  mm) and moderate ( $VAS>56$  mm) pain for all patients are shown in Table 7. Average every fourth patient had severe pain and every second patient had moderate or worse pain during the first postoperative week, regardless of analgesics. Pain was maximal on the fourth and fifth postoperative day (mean VAS of 46 mm).

**Table 7.** VAS (0-100 mm) values from day 1 to day 10 after surgery. Number of UPPP operated patients (n) with moderate to severe (VAS>30 mm) or only severe (VAS>56 mm) postoperative pain. Percentages are derived from the total population of 40 patients.

DAY	VAS > 30 mm	%	VAS > 56 mm	%
1	22	55	9	23
2	26	65	14	35
3	29	73	15	38
4	29	73	14	35
5	30	75	12	30
6	28	70	13	33
7	25	63	9	23
8	20	50	5	13
9	16	40	2	5
10	6	15	1	3

#### 5.2.4. Dietary intake after UPPP

The capability of the patients to drink or eat after surgery did not appear to be different between the laser-assisted and ultrasound scalpel-performed UPPP groups (respectively drink/eat: day 1 p=0.797/0.542; day 2 p=0.655/0.256; day 3 p=0.978/0.273; day 4 p=0.745/0.542; day 5 p=0.946/0.797; day 6 p=0.989/0.432; day 7 p=0.924/0.645; day 8 p=0.755/0.490; day 9 p=0.694/0.797; day 10 p=0.415/0.714). There was a significant improvement in the patients' ability to eat (p<0.001) and to drink (p<0.001) during the 10-day study period when all patients (n=40) were analyzed as a group (Figure 10). A significant improvement in eating and drinking occurred by days 8 (p=0.025 and p=0.034), 9 (p=0.001 and p=0.001) and 10 (p<0.001 and p<0.001) compared to the first postoperative day.



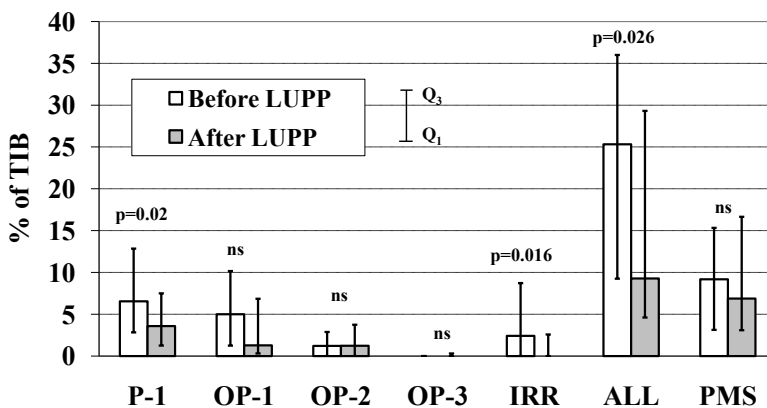
**Figure 10.** Postoperative average values for patients' ability to drink and eat (1=none, 2=moderately, or 3=sufficiently) from the day 1 to day 10. Each day value is composed of the average of 9.00 a.m., 3.00 p.m. and 9.00 p.m. values evaluated from the total population (n=40).

### 5.3. The efficacy of LUPP for velopharyngeal narrowing in patients with partial upper airway obstruction during sleep (III)

During the six-month follow-up the patients' mean weight decreased from 90 to 87.5 kg ( $p=0.037$ ) and BMI from 28.2 to 27.5 kg/m<sup>2</sup> ( $p=0.019$ ). Subjectively 88% of the patients reported improvement in snoring and 81% in daytime tiredness.

#### 5.3.1. SCSB and arterial oxyhemoglobin saturation findings

Preoperatively, the mean frequency of ALL was 26% of TIB. Consistent with the inclusion criteria, most of these (23% of TIB) were partial upper airway obstruction (IRR, P-1 and OP-1) and only 3% of TIB were episodes of obstructive apnea (OP-2 and OP-3) during sleep. In each individual patient ( $n=27$ ), partial obstruction represented more than half of the breathing abnormalities during sleep. The median percentages of the four types of periodic breathing and IRR before and after LUPP are shown in Figure 11. The median frequency of ALL decreased from 25.3 to 9.3% of TIB ( $p=0.026$ ). This reduction was due to significant decreases in P-1 and IRR. The median percentage of IRR decreased from 2.4 to 0.0% ( $p=0.016$ ) and of P-1 from 6.5 to 3.6% ( $p=0.02$ ). The other breathing abnormalities or PMS did not change significantly (Figure 11).



**Figure 11.** Distribution of breathing abnormalities recorded with SCSB. Patients had mainly episodes of partial upper airway obstruction during sleep. Median percentages, quartiles (Q1/Q3) and significant p-values of the four types of periodic breathing, IRR, ALL and PMS before and after LUPP are shown in the figure. Changes in obstructive periodic breathing types (OP-1,  $p=0.113$ ; OP-2,  $p=0.701$ ; OP-3,  $p=1.000$ ) and PMS ( $p=0.943$ ) were non-significant (ns).

Because PSG was not used, the diagnosis was based on other sleep parameters than AHI in this study with SCSB and therefore the success rate of Sher could not be counted. In an attempt to create a value similar to the Sher value, the individual SCSB derived raw-data was re-analyzed from the whole population ( $n=27$ ). The success rate was 52%, counted from the patients' periodic breathing patterns (P-1, OP-1, OP-2 and OP-3) and

IRR together. When only the partial upper airway obstruction patterns IRR, P-1 and OP-1 were considered, the success rate of LUPP was 56%.

The  $\text{SaO}_2$ min,  $\text{SaO}_2$ mean and  $\text{ODI}_4$  median values are given in Table 8. The reduction of  $\text{ODI}_4$  correlated with the reduction of the periodic breathing patterns P-1 ( $R^2=0.154$ ,  $p=0.043$ ), OP-1 ( $R^2=0.168$ ,  $p=0.034$ ), OP-3 ( $R^2=0.157$ ,  $p=0.042$ ) and ALL ( $R^2=0.255$ ,  $p=0.007$ ).

**Table 8.** Median values of  $\text{SaO}_2$ min,  $\text{SaO}_2$ mean and  $\text{ODI}_4$  before and six months after LUPP are presented. Quartiles show the highest value of first (Q1) and third (Q3) quartile. Statistical differences as p-values (p) calculated with Wilcoxon's signed rank test.

		$\text{SaO}_2^{\text{min}}$	$\text{SaO}_2^{\text{mean}}$	$\text{ODI}_4$
<b>Before LUPP</b>	<b>Median</b>	<b>84</b>	<b>95.8</b>	<b>3.7</b>
	Q1/Q3	76.5 / 88	94.9 / 96.9	1.1 / 7.5
<b>After LUPP</b>	<b>Median</b>	<b>85</b>	<b>95.4</b>	<b>2.3</b>
	Q1/Q3	82 / 87	94.8 / 96	1.1 / 4.9
<b>Difference</b>	<b>p</b>	<b>0.162</b>	<b>0.033</b>	<b>0.026</b>

### 5.3.2. Digital fluoroscopy findings

Upper airway imaging with digital fluoroscopy showed an increase of the minimal anteroposterior airway dimension at the velopharyngeal level postoperatively (Table 9). LUPP decreased the collapsibility at the velopharyngeal level, but not at the level of the oropharynx or the hyoid bone (data not shown).

**Table 9.** Minimum anteroposterior airway dimensions (ADmin) and airway collapsibility (Col) at the velopharyngeal (VP) and the oropharyngeal (OP) level before and six months after LUPP. The median value of ADmin (mm) and Col (%) based on digital fluoroscopy findings. Values of the first (Q1) and third (Q3) quartile are shown, p-values (p) according to Wilcoxon's signed rank test.

		Upper Airways			
		ADmin/VP	Col/VP	ADmin/OP	Col/OP
<b>Before LUPP</b>	<b>Median</b>	<b>3.8</b>	<b>13.8</b>	<b>9.8</b>	<b>12.4</b>
	Q1/Q3	0.5 / 5.2	0 / 43.9	7 / 13.2	3 / 21.3
<b>After LUPP</b>	<b>Median</b>	<b>4.5</b>	<b>2.5</b>	<b>10.3</b>	<b>12.2</b>
	Q1/Q3	3.6 / 5.8	0 / 14.8	7.2 / 14.8	5.7 / 18.2
<b>Difference</b>	<b>p</b>	<b>0.01</b>	<b>0.006</b>	<b>0.959</b>	<b>0.98</b>

### 5.3.3. Correlations

The changes in respiratory parameters did not correlate with changes in BMI, ADmin/VP or Col/VP (Table 10). The change in BMI did not correlate with change in ADmin/VP or Col/VP.

**Table 10.** P-values (p) of significantly changed respiratory parameters and BMI after LUPP are presented. Changes in the respiratory parameters after LUPP do not correlate with changes in BMI, ADmin/VP or Col/VP. All correlations are weak and non-significant.  $R^2$  = correlation coefficient.

	p	Correlation coefficients ( $R^2$ )		
		BMI	ADmin/VP	Col/VP
ODI <sub>4</sub>	0.026	0.09	<0.01	0.09
SaO <sub>2</sub> mean	0.033	0.04	<0.01	0.02
P-1	0.02	<0.01	0.07	<0.01
IRR	0.016	<0.01	0.04	0.05
ALL	0.026	0.01	<0.01	0.13
BMI	0.019	-	0.02	0.08

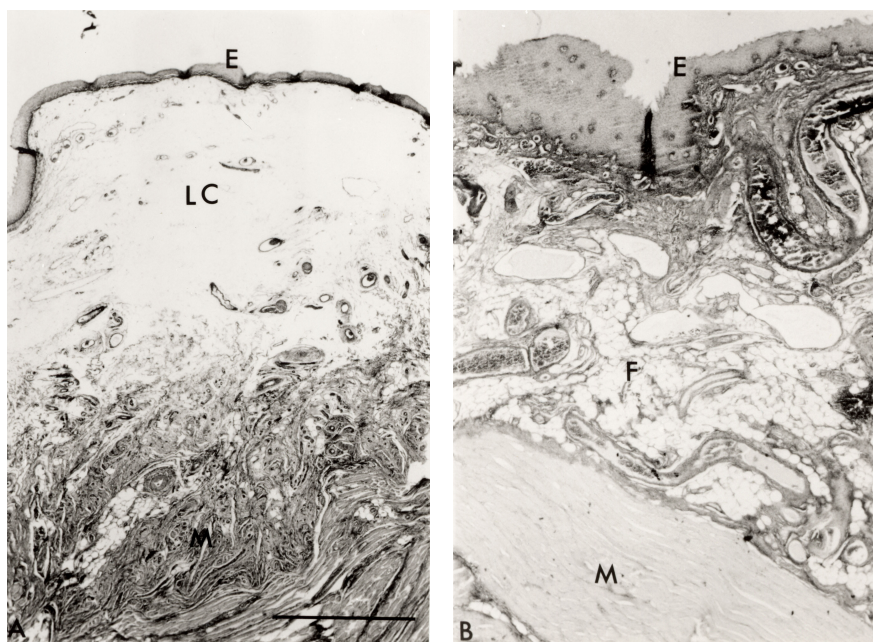
## 5.4. Body fat distribution and soft palate histology in patients with partial upper airway obstruction during sleep (IV)

### 5.4.1. Preoperative SCSB and arterial oxyhemoglobin saturation findings

The most common preoperative breathing abnormalities implied partial obstruction (P-1 = 7.5%; OP-1 = 7.6%; IRR = 5.1% of TIB). Partial obstruction constituted 82.5% and episodes of complete obstruction (OP-2 = 3.1%; OP-3 = 1.2% of TIB) constituted 17.5% of ALL (24.5% of TIB). The preoperative average ODI<sub>4</sub> was 5.6%, SaO<sub>2</sub>min 82.6% and SaO<sub>2</sub>mean 94.8%, respectively. ODI<sub>4</sub> correlated with all SCSB derived periodic breathing types and IRR (n=16; P-1, r=0.252, p= 0.347; OP-1, r=0.671, p<0.001; OP-2, r=0.802, p<0.001; OP-3, r=0.591, p=0.016; IRR, r=0.602, p=0.014).

### 5.4.2. Soft palate histology

13 out of 16 soft palate specimens fulfilled the quality criteria for histological analysis. Characteristic for the specimens was a marked proportion of loose connective tissue (17.1%±11.4) as shown in a representative sample (A) in Figure 12. The proportion of fat tissue was much less (3.2%±2.6). There was a significant correlation between loose connective tissue and the SCSB markers for partial obstruction (n=13; OP-1, r=0.758, p=0.0026; IRR, r=0.591, p=0.0332). The loose connective tissue did not correlate with any other SCSB markers or with ODI<sub>4</sub> (n=13; P-1, r=0.394, p=0.183; OP-2, r=0.0824, p=0.789; OP-3, r=0.0944, p=0.759; ODI<sub>4</sub>, r=0.0514, p=0.868). The percentage of fat, compact connective, glandular, muscle or lymphatic tissues in the uvular specimens did not correlate with body fat distribution (W/H-ratio, BMI, BIA and skinfold derived fat percentage) or SDB (IRR, P-1, OP-1, OP-2, OP-3 and ALL) or ODI<sub>4</sub>.



**Figure 12.** **A.** Uvula from a patient with partial upper airway obstruction presents with a high proportion of loose connective tissue (LC), which appears as a pale staining area between the epithelium (E) and striated muscle (M). This histological appearance is compatible with marked tissue edema. Scale bar=1 $\mu$ m. **B.** Uvula from a patient with severe OSAS, compare to A. Note a high proportion of fat tissue (F) beneath the epithelium (E).

#### 5.4.3. Body fat estimation

Comparative techniques were used to estimate the body fat content and fat distribution of patients with partial upper airway obstruction during sleep. According to Pearson's correlation matrix analysis, BIA did not correlate with skinfold thickness ( $r=0.327$ ,  $p=0.217$ ). Despite this inconsistency, both BIA and skinfold derived fat percentage separately correlated with the conventional body fat markers, BMI ( $n=16$ ; BIA,  $r=0.747$ ,  $p<0.001$ ; skinfold fat percentage  $r=0.572$ ,  $p=0.021$ ) and the W/H-ratio ( $n=16$ ; BIA,  $r=0.649$ ,  $p=0.007$ ; skinfold fat percentage,  $r=0.515$ ,  $p=0.041$ ). The BMI correlated positively with age ( $n=16$ ;  $r=0.586$ ,  $p=0.017$ ) and the W/H-ratio ( $n=16$ ;  $r=0.734$ ,  $p=0.0012$ ). BMI was the only body fat distribution measurement that correlated with SDB ( $n=16$ ; OP-2,  $r=0.573$ ,  $p=0.0202$ ; IRR,  $r=0.627$ ,  $p=0.0093$ ).

## 6. DISCUSSION

OSAS as a cause of daytime sleepiness, impaired quality of life and cardiovascular comorbidity has only recently been recognized among the lay population. Too narrow upper airway is the most common cause of SDB. Therefore, surgical correction of the structural upper airway abnormalities was initial and natural approach to treat patients with OSAS and socially disturbing snoring. Nasal CPAP has later become primary treatment, particularly of obese patients with moderate to severe OSAS. The focus of upper airway surgery has moved from treating severe OSA toward milder forms of upper airway obstruction, where prevention of aggravation of SDB is the primary purpose. It has been shown that there is natural tendency of mild OSA for aggravation of apneas and symptoms if untreated. Surgical treatments may show as good results as CPAP after several years of follow-up without changes in BMI (Sahlman et al. 2007). This is strengthened by the finding that in mild OSAS patients active surgical treatments reduce OSA-related symptoms (Sahlman et al. 2009).

Almost all studies in the literature focus on the AHI or arterial oxyhemoglobin desaturation indexes. This is due to a lack of methodology to detect or diagnose non-apneic breathing abnormalities during sleep. The present studies exploited the advantage of the availability of the SCSB which offered a unique opportunity to evaluate the treatment response of partial upper airway obstruction during sleep to surgery. The pathophysiology of partial upper airway obstruction during sleep is not sufficiently understood. It has previously been thought to present a mild form of OSA or an early stage of developing OSA. According to recent thinking partial upper airway obstruction may progress either to a more severe degree of partial upper airway obstruction or change to OSA. In part of the patients it is also possible that end-stage OSAS may lead to partial upper airway obstruction and hypercapnic respiratory failure. The present studies were not designed to assess the long-term evolution of partial upper airway obstruction during sleep. They focused on partial upper obstruction during sleep in terms of its response to surgery. Large-scale follow-up studies are needed to evaluate whether the initial improvements obtained with surgery of partial obstruction later relapse or will prevent subsequent aggravation.

### 6.1. Tracheostomy as a treatment of obstructive sleep apnea

Tracheostomy was initial and effective treatment in the history of OSA approved by clinicians. Studies have showed that tracheostomy is efficacious in terms of PSG and mortality. We decided to choose a therapeutic approach that excluded all the upper airways, tracheostomy, for showing the overall efficacy of surgery in OSAS patients. We used the SCSB to examine patients with severe OSAS with or without partial upper airway obstruction during sleep.

Tracheostomy has been evaluated to some degree previously with various parameters ranging from AHI to SaO<sub>2</sub> and with follow-up studies on mortality and morbidity. These studies have shown a similar mortality trend for tracheostomized OSAS patients in long-term follow-up studies (Partinen 1988b, Thatcher and Maisel 2003) as in the present postoperative study covering an average follow-up of four years. All patients in this study population considered surgery absolutely necessary, regardless of morbidity due to mucous overproduction, granulation formation and occasional respiratory infections. Findings in the literature are similar concerning long-term tracheostomy to treat OSAS patients (Browaldh 2008). The success of tracheostomy has been measured with AHI and by this standard tracheostomy is highly effective among obese patients with severe OSAS (Guilleminault 1981, Ledereich et al. 1995, Kim et al. 1998). The success of surgery has also been demonstrated in terms of less arterial oxyhemoglobin desaturation (Browaldh 2008). In the present study, tracheostomy was unequivocally beneficial, since it eliminated almost all obstructive apneas and increased significantly oxygen saturation levels. However, there were signs of an increasing tendency for central apneas as the obstructive apneas were reduced following tracheostomy. It is possible that these central apneas in conjunction with hypoventilation and hypoxemia were part of lacking pulmonary decompensation, a phenomenon reported in the literature (Fletcher et al. 1989, Kim et al. 1998).

In this follow-up study the efficacy of tracheostomy was characterized by the disappearance of obstructive sleep apnea episodes during sleep in the SCSB recordings and increased arterial oxygen saturation levels in conjunction with a positive development in sleep related symptoms, depression and general health. All tracheostomy patients considered the tracheostomy absolutely necessary.

For symptomatic patients with severe OSAS and for who the maintenance of CPAP treatment is not feasible elective tracheostomy in local anaesthesia is one possible treatment if long-term dieting is not successful and no other surgical treatments are possible.

## **6.2. Partial upper airway obstruction during sleep**

The initial study was performed in patients who had severe OSAS and severe obesity which necessitated a tracheostomy. However, the majority of patient presents with less severe forms of SDB. Surgery could be a treatment alternative to nasal CPAP, in particular to patients without severe obesity. When studied with the SCSB, many patients with mild to moderate SDB present with few episodes of obstructive sleep apnea during sleep but prolonged episodes of partial upper airway obstruction during sleep. Since the literature does not provide evidence on whether these patients benefit from surgery, these studies were initiated. The main part of this thesis focused on non-morbidly obese patients presenting with a predominantly partial upper airway obstruction during sleep.



### **6.2.1. Measurement of partial upper airway obstruction during sleep with SCSB**

The present studies did not use the standard, internationally accepted methodology for studying sleep and breathing. Instead of PSG and oronasal thermistors for measurement of airflow and thoracoabdominal belts for measurement of the respiratory drive, the SCSB was used. This methodology was chosen for several reasons. First, at the time of the studies, the SCSB had established its position as a cost-beneficial approach to diagnose SDB at the Turku University Central Hospital. With limited resources for diagnostics and evaluation of treatment responses, the SCSB enabled a large number of patients to be followed-up. Although not widely accepted, the method had already been extensively evaluated and validated for its purpose by several research groups at the Turku University and elsewhere (Alihanka et al. 1981, Polo et al. 1988). The possibility to record partial upper airway obstruction during sleep was a unique and pioneering feature in this field, the importance of which is still not fully appreciated. These simplified cardiorespiratory recording systems have largely replaced the expensive PSG recordings, at least in Europe. Inspiratory flow limitation shown by the nasal pressure signal has finally aroused wider interest in partial upper airway obstruction during sleep (Aittokallio et al. 2001). The SCSB offered the possibility to our research group to perform pioneering studies on partial obstruction ahead of its time.

The major disadvantage of the SCSB is that it is not widely known by the scientific community and only few researchers have sufficient experience in how to interpret the readings correctly. This will certainly limit the number of referrals to the present studies. There are studies ongoing on the sensitivity and specificity of the SCSB method for detection of increased intrathoracic pressure variation during episodes of apnea, hypopnea and partial upper airway obstruction during sleep. There are also new developments of the SCSB recording techniques allowing wireless long-term monitoring at low cost. Moreover, recent other recording techniques, including inspiratory flow shape analysis (Aittokallio et al. 2001) and transcutaneous CO<sub>2</sub>, have increased our understanding of the pathophysiology of partial upper airway obstruction during sleep (Rimpilä et al. 2010). This new knowledge has increased the feasibility and credibility of the SCSB technique (Polo 1992).

### **6.2.2. Efficacy of LUPP to reduce partial upper airway obstruction during sleep**

Patients with partial upper airway obstruction during sleep as the predominant form of SDB responded well to LUPP. The frequency of all breathing abnormalities diagnosed with SCSB decreased and the patients' subjective daytime sleepiness reduced. The problematic residual SDB was of minor concern, as the inclusion criteria for surgery were related to partial obstruction parameters. The tissue saving soft palate surgery (LUPP) reduced partial upper airway obstruction in patients with retropalatal narrowing.

There are no previous studies on the role of upper airway surgery to treat partial upper airway obstruction during sleep. According to a previous CT study, the upper airway size of the patients with partial upper airway obstruction did not differ from controls

at the level of the soft palate (Polo et al. 1991). In contrast to patients with OSAS, the structural narrowing occurs essentially at the level of the hyoid bone and tongue base. A priori, this observation would suggest that the soft palate would not be the optimal target for surgery. This idea was also supported by the observation that UPPP transformed severe obstruction into partial upper airway obstruction during sleep (Polo et al. 1989). However, in the present study, evaluated exactly with the same diagnostic method as the earlier studies, patients with initially partial upper airway obstruction as the predominant respiratory abnormality during sleep were successfully treated with LUPP. There are several possible explanations for this. In this study, the patient population was essentially non-obese and the overall frequency of breathing abnormalities was not very high. The decrease in frequency of pathological breathing patterns was not explained by the decrease in BMI. The soft palate level seems to be a critical determinant of SDB even in patients with partial upper airway obstruction during sleep. LUPP was unlikely to have any effect at the lower levels of upper airway. Thus, correction of the narrowing at the soft palate level may suffice to improve gas exchange to a degree that respiratory efforts do not increase and partial upper airway obstruction does not occur during sleep. The finding that the respiratory efforts do not need to increase during sleep could also explain the reduced daytime sleepiness (Pelin et al. 2003, Svensson et al. 2008).

In the earlier study by Polo and colleagues the obstructive apnea events (OP-3) detected with SCSB decreased from 56.3% to 18.4% of TIB during sleep after UPPP including tonsillectomy in OSAS patients (Polo et al. 1989). In present study, the values of the SCSB parameters indicating partial upper airway obstruction during sleep declined (from 14% to 4.9%) after LUPP, as IRR and P-1 were reduced significantly and OP-1 showed a clinically relevant but statistically not significant decline. These differences are in line with the chosen study populations. In the earlier study by Polo and colleagues the other breathing abnormalities of the SCSB patterns tended to increase simultaneously in proportion with a strong correlation with a reduction of OP-3 values (Polo et al. 1989). They found that 72% out of the OP-3 reduction was transformed postoperatively into less severe forms of abnormal breathing patterns and only 28% of OP-3 disappeared completely after UPPP. In the present study, a reduction in partial obstruction parameters contributed further to a significantly reduction in the frequency of ALL (from 25.3% to 9.3%) during the night, as the occurrence of obstructive episodes (OP-2 and OP-3) after LUPP remained almost unchanged. In the earlier study by Polo and colleagues the total number of ALL during night was decreased from 86.2% to 75.6% (Polo et al. 1989). Thus, a biologically significant amount of SDB remained after the operation and, interestingly, the IRR reflecting partially obstructed upper airway, was the only parameter that increased significantly. This supports the thinking that operative treatment may be more likely to be successful when performed for patients with less severe upper airway obstruction during sleep to prevent residual respiratory abnormality.

A Sher-imitating surgical success rate estimated from SCSB findings showed a positive tendency after LUPP in this study population with partial upper airway obstruction during sleep, since more than 50% of ALL disappeared. Thus, LUPP in this population had good

efficacy and was comparable to studies evaluating UPPP in OSAS with PSG. Whether the Sher-imitating surgical success rate is valid for partial obstruction is controversial. After all, the sleep study and diagnosis system criteria are different between PSG and SCSB. However, the population in this study had partial upper airway obstruction during sleep and therefore this discussion is relevant only for studies employing similar respiratory analysis methods.

If a patient remains symptomatic postoperatively, but AHI is less than 5/h the patient may have breathing abnormalities not detected with PSG. Therefore, techniques showing increased respiratory efforts during partial obstruction are essential when recording breathing during sleep in such patients.

### **6.2.3. LUPP and arterial oxyhemoglobin saturation**

The  $\text{SaO}_2\text{min}$  and  $\text{SaO}_2\text{mean}$  were improved in patients operated on for severe OSAS according to Polo and colleagues (Polo et al. 1989). However, desaturation events continued to occur after UPPP, suggesting presence of some residual sleep pathology. In this study, patients with partial upper airway obstruction during sleep did not have postoperatively markedly raised arterial oxygen saturation levels. The  $\text{SaO}_2\text{min}$  was at the same level postoperatively and  $\text{SaO}_2\text{mean}$  showed even a decreasing tendency, which could be the result of a lack of central stimulation of ventilation. This theory is based on the relief of narrowed structures in the soft palate region caused by LUPP, while preoperatively saturations were higher due to elevated  $\text{CO}_2$ , the main activator of ventilation, and inspiratory efforts were stronger due to persistent obstruction. Postoperatively, after the relief of anatomical obstruction, the amount of  $\text{CO}_2$  is reduced and the stimulus for ventilatory efforts becomes weaker which reduces slightly lowered  $\text{SaO}_2\text{mean}$ . However,  $\text{ODI}_4$  was significantly reduced and correlated well with both obstructive periodic breathing and partial upper airway obstruction patterns during sleep, supporting the power of SCSB to detect pathological sleep that affects respiration. The decrease in  $\text{ODI}_4$  can be considered clinically significant as the level of preoperative and postoperative arterial saturation was close to normal. This finding was supported by decreased symptoms. The same capacity of SCSB was seen regarding the  $\text{ODI}_4$  and SCSB parameters in study IV, where IRR and all obstructive periodic breathing type patterns during sleep had a strong correlation. Hence, it seems that  $\text{ODI}_4$  is a sensitive parameter when used together with SCSB both before and after surgery for sensitive analysis of sleep disturbances in patients with partial upper airway obstruction during sleep.

### **6.2.4. Upper airway imaging**

Digital fluoroscopy was used in this study for upper airway imaging. The advantage of this technique was that the dynamics of the entire upper airway in the supine position could be recorded as a lateral fluoroscopic view over the course of several respiratory cycles with 6.3 images per second. By digital subtraction and edge enhancement techniques,

soft tissue contours outlining the airway could be visualized with high precision. Digital fluoroscopy does not display any particular slice of the upper airway but summarizes the upper airway contour into one image. Therefore, precise positioning of the patient and slice selection are not issues with digital fluoroscopy. Digital fluoroscopy is faster and there is less irradiation than with CT and it offers benefit for the cost also.

The imagine study was done while the patient was awake and supine. Imaging during natural or induced sleep could have resulted in more accurate results. These interventions were, however, considered too demanding and risky for the purpose of the study. However, dynamic upper airway imaging has shown that the upper airways of snorers with and without OSAS are more collapsible than of subjects without SDB, even during awake respiration (Schwab et al. 1993).

Tsushima and colleagues reported that the collapsibility at the velopharyngeal level was smaller among healthy subjects when compared with patients presenting with partial upper airway obstruction during sleep (Tsushima et al. 1996). In this study, LUPP decreased the upper airway collapsibility at the velopharynx, which was the target of the operation for patients with partial upper airway obstruction during sleep. As expected, the collapsibility at the oropharyngeal and hyoid bone levels was unchanged after LUPP. The decreased velopharyngeal collapsibility should be closely related to removal of tissue, which could also be demonstrated by upper airway imaging. However, in the study of Polo and colleagues, despite a significant reduction in obstructive apnea episodes after UPPP, upper airway CT while awake did not provide any evidence of enlargement of the velopharyngeal airway (Polo et al. 1989). This finding casts doubts as to whether UPPP ultimately acts more on upper airway function, such as collapsibility, than on structure. The negative structural response to UPPP in the earlier study by Polo and colleagues could be explained by the finding that their patients had postoperatively still severe OSAS and increased partial upper airway obstruction (IRR). According to some other studies involving patients with OSAS, uvulopalatal surgery increases the postoperative retropalatal space evaluated with CT (Shepard and Thawley 1989, Li et al. 2005). Also in this study, patients with partial upper airway obstruction during sleep had enlarged anterior-posterior measures of the upper airways at the velopharyngeal level after LUPP, as shown by the digital fluoroscopy.

In the study by Tsushima and colleagues the upper airways were more collapsible in OSAS after LUPPP in poor responders at the velopharyngeal level than in good responders (Tsushima et al. 1997). Despite this finding, the value of collapsibility as a predictor of the result of LUPPP was low, since no difference between these two groups was observed preoperatively. According to these findings, digital fluoroscopy at the velopharyngeal level cannot be used as a predictor of surgery but it does demonstrate the outcome.

LUPP reduced both collapsibility and respiratory abnormalities, but there was no relation between these changes. It is possible that when retropalatal narrowing is relieved with LUPP, the positive treatment effect is mediated by beneficial effects at other levels of

the upper airways. This could be due to decreased negative intraluminal pressure during inspiration, resulting in less dynamic narrowing induced by Bernoulli's effect. Some authors have suggested that the effect of UPPP is mediated by a decreased BMI. The BMI of patients in this study decreased also after operation, but the BMI changes did not correlate with changes in collapsibility.

It seems likely that upper airway obstruction during sleep has a multifactor complex etiology. In addition to upper airway structure and collapsibility, other factors, e.g., respiratory drive, sympathetic activity, muscle relaxation or sleeping position, are involved.

### **6.3. Comparison of ultrasound scalpel and laser-assisted UPPP**

The feasibility of using the ultrasound scalpel for UPPP in patients with SDB has not been assessed before. All previous reports in the literature evaluating this method deal with other surgical targets, such as the palatal tonsils. None of them compares ultrasound scalpel with laser-assisted surgery. We compared this technique with laser-assisted surgery with regard to three aspects: firstly, the degree of pain caused by performing the operation with different techniques was assessed in terms of the need of postoperative pain medication, adequacy of pain relief and dietary intake during convalescence after surgery. Secondly, perioperative bleeding, operating room time and duration of the operation together with histological injury to soft palate were analyzed. Thirdly, all possible untoward medical occurrences such as postoperative haemorrhage events were recorded during the 10-day study period after UPPP.

There were fewer haemorrhagic events after UPPP when the ultrasound scalpel was used, but there did not appear to be any benefit in terms of reduced blood loss during operation. The operating time and the operating room time were equal with both techniques. Also the degree of postoperative pain and the capability of the patient to drink or eat were similar. The patients' overall dietary intake increased markedly during the last two days of the 10-day follow-up period. The increased dietary intake was associated with reduced in daily pain.

This is the first study to analyze the uvulopalatal tissue damage associated with the ultrasound scalpel. It has been proposed that the ultrasound scalpel causes less tissue damage next to the cutting line. We did not find any support for this suggestion, since the coagulation tissue injury in the removed specimens was 0.05 mm deeper with ultrasound scalpel than with laser. The use of the ultrasound scalpel did not provide any benefits when used in the soft palate area in terms of tissue saving compared to laser-assistance.

### **6.4. Pain medication after UPPP**

UPPP is associated with severe postoperative pain in the operated area. Therefore optimizing pain control is important for improving the convalescence after UPPP. In this study we compared the degree of postoperative pain and need of pain medication. For

pain analysis, all patients were analyzed as one group, irrespective of which operation technique was used.

A number of reports deal with postoperative pain management and pain analysis after UPPP or LUPPP. The most frequently used analgesics have been acetaminophen, NSAIDs and weak opioids such as tramadolhydroxylate.

In this study most UPPP patients had moderate (VAS>30 mm) postoperative pain and average every fourth patient had severe (VAS>56 mm) pain during the first postoperative week. The postoperative pain occurring in patients of this study was similar as reported by Nikanne and colleagues in an earlier study (Nikanne et al. 2003). They reported severe pain (VAS>50 mm) at day 5 after UPPP with electrodissection in half of their patients. Troell and co-workers performed electrocautery UPPP and reported a mean VAS of pain of 5.5 at day 5 (Troell et al. 2000). The observations in the present study were very similar: the highest mean VAS score (4.6) was recorded on day 4 and day 5 after surgery.

Pain at the end of the follow-up period was separately evaluated by both Troell and co-workers and Nikanne and co-workers (Troell et al. 2000, Nikanne et al. 2003). Troell and colleagues reported a mean VAS of pain of 3.8 on day 10 following surgery: the patients took acetaminophen. In the study by Nikanne and colleagues there was discomfort due to slight (VAS>16 mm) or more severe pain for up to two weeks in 39% of the patients who took ketoprofen for analgesia (mean VAS 0.6 on day 14). The VAS score in the present study was 1.7 at the end of the follow-up period (day 10).

The degree of diurnal pain was assessed for all 40 patients in this study and it was found that the pain values were significantly higher at 9.00 a.m. than during the rest of the day, probably because the first analgesic medication of the day had not yet been taken. Nikanne and colleagues reported similar findings and concluded that using only ketoprofen capsules orally every 30 minutes at a maximum dose of 5 mg/kg/day for analgesia was not sufficient for ensuring undisturbed sleep (Nikanne et al. 2003).

In the present study some patients had severe pain. This was probably due to the finding that these patients preferred not to use adequate doses of naproxen suppositories, which was standard postoperative analgesic. Because of painful swallowing, also oral administration of water soluble acetaminophen-codeine tablets was poor and provoked even more pain. Of all patients operated on for UPPP, 20% (8/40) reported overall discomfort because of inadequate pain medication despite the high use of acetaminophen-codeine tablets.

Significant postoperative pain after UPPP remains problematic. NSAIDs with a prolonged effect in the evening could be an option for resolving the most important postoperative problem after UPPP, namely the long-lasting and marked pain. For some patients weak opioids in drop form could be used as well as strong opioid patches. In the future, the

use of a proper standardized protocol to assess pain should be considered in cases of predictable severe postoperative pain or major surgery.

### **6.5. Histology of soft palate and body fat distribution**

Previous morphological studies have reported histological findings of obese subjects with OSAS. Stauffer and colleagues made an autopsy study of obese patients with severe OSAS and concluded that the uvula fat and muscle percentages are higher in OSAS patients than in controls (Stauffer et al. 1989). They also found a correlation between the fat content of the uvula and the frequency of apnea and hypopnea episodes. However, non-apneic snorers in the patient group had a similar morphology as patients with OSAS. Because of this finding it could be assumed that patients with various severity of SDB do not differ with regards to their histopathological findings. Zohar and co-workers studied OSAS patients and control cadavers but there were no correlation between a semiquantitative evaluation of fat deposition and BMI or AHI despite excessive fat tissue infiltration in the soft palate region among patients (Zohar et al. 1998). Paulsen and colleagues found changes in the connective tissue level and a more diffuse infiltration of leukocytes inside the lamina propria among OSAS patients when compared to cadavers (Paulsen et al. 2002). This finding supported their hypothesis of structural changes in the mucosa caused by the trauma of snoring and further leading to upper airway collapsibility. However, they did not find any correlation between respiratory parameters and edema suggesting findings unlike in the present study.

There are certain problems when using only cadavers as controls. First, as autolysis and dehydration of tissues starts immediately after death, post-mortem changes may have occurred before histological investigation starts, which does not occur when tissue samples are removed during surgery and fixed instantly. Another problem is the possibility that the illness related to the death of the subject may activate changes in the tissues. Probably the main issue using cadavers as controls is the lack of knowledge about any previous SDB, since a recent sleep study data is rarely or never available. Therefore, comparison between samples and histology collected from patients and cadavers remains challenging.

Woodson and colleagues made a qualitative comparison of patients with severe OSAS, snorers presenting with AHI less than 20/h and non-snorers (Woodson et al. 1991). They concluded that no distinctive histopathologic findings could be associated with the development of OSA. However, two groups have demonstrated histopathological finding of extensive edema in the entire lamina propria. Berger and co-workers studied male patients with OSAS and found more connective tissue, i.e. edema, in the moderate apnea group compared with the group with severe OSAS (Berger et al. 2002). Hamans and colleagues investigated OSAS patients and non-apneic snorers (Hamans et al. 2000). Both patient groups presented with similar amounts of intercellular space despite the clinical severity of OSAS. An edematous appearance was observed in the submucosal

part of the uvula specimens. According to these previous studies, it may be assumed that tissue edema occurs in the uvulopalatal region in patients with OSAS and probably also in non-apneic snorers. There were no correlation between BMI and fat tissue histopathology in studies of Berger and colleagues nor Hamans and colleagues. These findings support the theory that the amount of uvulopalatal fat tissue is not dependent on BMI or OSA.

The soft palate fat may play an important role only in morbidly obese ( $\text{BMI} \geq 40 \text{ kg/m}^2$ ) patients, while in subjects with less obesity, the tissue content such as intercellular space, i.e. connective or loose connective tissue, could be more important cause of excessive airway obstruction in the edematous uvulopalatal region. In the present study, histological analysis of the resection specimens showed only 3.2% of adipose tissue, which suggests that fat accumulation is not needed for manifestation of partial upper airway obstruction during sleep. Particularly less obese subjects may have velopharyngeal tissue edema due to loose connective tissue, which is associated or contributing with the manifestation of partial upper airway obstruction during sleep. Similar findings were shown in previous studies of Hamans and colleagues and Berger and colleagues, although without correlation to findings of sleep studies (Hamans et al. 2000, Berger et al. 2002). Puig and colleagues demonstrated in a cell culture with human bronchial epithelial cells that mechanical vibration stimulated the inflammatory cascade, as reflected by increase in interleukin-8 (Puig et al. 2005). This finding supports the hypothesis that snoring could contribute to airway inflammation in SDB. This inflammation could trigger the histological changes seen in the connective tissue.

The amount of loose connective tissue may increase as a result of mechanical trauma caused by snoring and tissue vibrations, negative air pressure during IRR or obstructive periodic breathing in the upper airways. In this study, the histology of uvulopalatal tissue specimen showed edema manifested in the uvulopalatal region as loose connective tissue. Irrespective of the cause of partial upper airway obstruction during sleep, edema in the uvulopalatal region might be factor that further aggravates airway narrowing. The role of loose connective tissue for the manifestation of breathing abnormalities during sleep is further corroborated by the loose connective tissue content correlation with partial upper airway obstruction parameters (IRR, OP-1) in the present study group of patients with  $\text{BMI} < 35 \text{ kg/m}^2$ . In a previous study, parallel with reduced frequency of apnea episodes of LUPPP-operated patients with OSAS there was an increase of volume of the nasal cavity (Antila et al. 1997). This finding demonstrates decreased edema even in other parts of the upper airway as a result of recovery after surgery. These observations and hypotheses are in the line with the thinking that limited surgery at an early stage of upper airway narrowing might possibly eliminate the self-aggravating process of snoring-induced upper airway remodelling, which finally could develop into OSAS in some patients.

Obesity, particularly central body fat accumulation (visceral fat), has been regarded as the most common finding in patients with OSAS. In this study the most common methods



were used to estimate body fat content and fat distribution in patients with partial upper airway obstruction during sleep. This study showed that even in a group of less obese patients there was a correlation between BMI and partial upper airway obstruction during sleep, but this correlation was not explained by the amount of uvulopalatal fat tissue. Interestingly, the uvulopalatal fat tissue did not correlate with the findings of body fat distribution and breathing abnormalities.

Patients with partial upper airway obstruction during sleep present with uvulopalatal edema which is manifested in the uvulopalatal region as loose connective tissue. Although partial upper airway obstruction during sleep also increases with increasing BMI, the loose connective tissue may play a more important role than the soft palate fat accumulation in partial upper airway obstruction during sleep. Velopharyngeal edema may play a role needed for the initiation and aggravation of the upper airway obstruction resulting in symptomatic partial or complete upper airway obstruction during sleep.

## **6.6. Upper airway surgery for sleep-disordered breathing – is there a future?**

The technique of the nasal CPAP has developed and emerged as first line therapy for moderate and severe OSAS patients. Because of its other favorable effects on lung function in obesity, CPAP is also the treatment of choice for symptomatic SDB of any severity associated with marked obesity. Recently, UPPP is performed much less often than two decades ago. The enthusiasm for upper airway surgery to treat OSA has decreased for some reasons. The results of surgery may be unpredictable and the long-term success rate is lower than in case of CPAP, particularly in obese patients. With our present knowledge of the treatment outcomes it is important to ask, if there is a future for upper airway surgery in the treatment of SDB.

Today, upper airway surgery is still needed to correct specific structural abnormalities primarily in lean patients with OSAS, especially in case of rejection of nasal CPAP. In the future the focus of surgery could be early intervention to prevent aggravating OSA. There are a number of challenges for further research before preventive upper airway surgery for SDB is established in current practise. First, we need more understanding about the pathogenesis of SDB, particularly on the interactions between upper airway structure, respiratory airflow and breathing control. This requires more sophisticated diagnostic methods to monitor airflow, the dynamic processes of the upper airway during sleep and the impact of the autonomic nervous system on sleep and metabolism. A multidisciplinary approach involving surgeons and other medical and engineering experts is needed.

The present study is the first in the literature that addresses the effect of surgery on partial upper airway obstruction during sleep. This condition is objectively measurable form of SDB and is distinct from OSA and AHI. With AHI as the only diagnostic measure, there is no comprehensive understanding of the pathophysiology of SDB. However, this work

is only an opening to the field of demonstration and treatment of the early stages of upper airway dysfunction during sleep.

There is need to establish early clinical predictors of SDB with more sensitive diagnostic methods. Using such advanced techniques we could assess certain surgical methods with better success and reverse more likely the evolution of upper airway dysfunction. With curative surgery there would be less need for nasal CPAP to treat patients presenting fully developed OSAS with cardiovascular co-morbidities.

## 7. CONCLUSIONS

- I Permanent tracheostomy improved respiratory parameters during sleep and declined obstructive apnea episodes in patients with severe OSAS. The total bypass of all upper airway obstruction sites, by use of a tracheostomy, is an adequate treatment in severe OSAS patients.
- II The ultrasound scalpel and laser-assisted techniques were equal for UPPP. Only the lower incidence of postoperative haemorrhage events slightly supports the use of ultrasound scalpel in pharyngeal surgery instead of laser-assistance.
- III The postoperative significant pain lasting over one week after UPPP was a challenge for analgesic treatment. Pain control is demanding in the area of pharynx that cannot be immobilized after surgery.
- IV Partial upper airway obstruction during sleep and  $ODI_4$  decreased after LUPP in patients without severe obesity. This was followed by the significantly decreased collapsibility at the preoperatively narrowed velopharyngeal level, where the LUPP was made. LUPP provides efficient therapy among selected patients with partial upper airway obstruction during sleep.
- V There are other factors than fat accumulation in the soft palate level that contribute to early aggravation of partial upper airway obstruction during sleep. Tissue edema (the loose connective tissue) was the only histological finding that correlated with the partial upper airway obstruction parameters during sleep. Tissue vibration and/or negative airway pressure caused edema may be the primary cause of narrowing in the upper airway.

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A handwritten signature in black ink, consisting of a large, sweeping loop on the left side that crosses over itself and extends into a long, horizontal stroke to the right.

Perttu Halme

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