Obstructive Sleep Apnea Syndrome

Pathogenetic Aspects and Treatment

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Obstructief Slaapapneusyndroom

Pathogenetische Aspecten en Behandeling

Proefschrift

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CONTENTS

CHAPTER 6 Quality of Life in Patients with Obstructive Sleep Apnea Syndrome

CHAPTER 7 General Discussion and Conclusions

CHAPTER 1

Introduction to the Obstructive Sleep Apnea Syndrome

1.1 Introduction

Almost twenty years ago obstructive sleep apnea was considered to be a medical curiosity that was of little importance, and snoring was merely the subject of humor than one of serious investigation. Although the clinical manifestations of sleep apnea syndrome have been described as early as in the fat boy Joe in Charles Dickens Pickwick Papers, it was Gastaut in 1965 who provided the first detailed polygraphic description of the manifestations of this sleep related breathing disorder (1,2).
Since that date countless studies have been performed and published, concerning all possible aspects of sleep apnea syndrome. Epidemiological and clinical research revealed that the obstructive sleep apnea syndrome may be considered a major public health problem and that the sequelae of the syndrome may have devastating consequences for the lives of those affected (3), but the long term sequelae of obstructive sleep apnea need further elucidation in well designed studies (4).
This chapter provides a review of prevalence, pathogenesis, natural history, symptomatology, diagnosis and treatment of Obstructive Sleep Apnea Syndrome (OSAS). First a brief description of the spectrum of sleep related breathing disorders is given.

1.2 Sleep Related Breathing Disorders

Through the years different names and synonyms have been used in describing rather similar aspects of sleep related breathing disorders (SRBD) (5). The term "Pickwickian syndrome", a presumed form of obstructive sleep apnea with obesity, CO_2 retention and diminished ventilatory drive has been applied to different sleep related breathing disorders, as has the term obesity hypoventilation syndrome. These terms should not be used any more. A very rare form of SRBD is "Ondine's curse" with primary failure of the medullary automatic respiratory centre resulting in hypoventilation and central apnea. Patients with Ondines curse are dependent on nocturnal artificial ventilation. Although primary forms are believed to exist, this disorder is generally associated with acquired medullary dysfunction after trauma or infection. The Pickwickian syndrome and Ondine's curse are now classified under the central alveolar hypoventilation syndroms (6).
An apnea has since 1976 been defined as cessation of airflow at the nose and mouth lasting at least ten seconds (7). We distinguish three types of apneas. Central apneas consist of cessation of airflow and cessation of ventilatory effort. Obstructive apneas consist of cesssation of airflow through nose and mouth while inspiratory effort is still present. Mixed apneas consist of both central and obstructory events, usually starting as central and proceeding into obstruction.

Snoring is characterised by inspiratory breathing sounds originating in the collapsible part of the upper airway (8). Mild desaturations may be present, but this is not a characteristic of this disorder. By the age of 60, approximately 60% of men and 40% of women will snore habitually (almost every night) (9).
Central sleep apnea syndrome, which in its pure form is a rare disorder, is characterised by cessation or decrease of ventilatory effort during sleep causing central apneas, usually resulting in oxygen desaturation. Obstructive apneas and snoring can be present. Excessive daytime sleepiness is a common complaint. Sleep is generally disturbed by frequent awakenings, leading to an inability to maintain sleep and patients often arouse with a sense of choking. Cardiovascular disease, cerebrovascular disease and other neurological damage affecting the central control of respiration are contributing and sometimes causative factors. The repetitive central apneas are related to the physiologic interaction between the pulmonary system and the central nervous system within the feedback loop of the respiratory control system, as is seen in Cheynes Stokes breathing.
Central alveolar hypoventilation syndrome, sometimes referred to as primary alveolar hypoventilation, is characterised by ventilatory impairment, resulting in arterial oxygen desaturation. This disorder occurs in patients with normal mechanical properties of the lung. Obstructive and central apneas can occasionally be present, but are not predominant. Inability to maintain sleep with insomnia may result. A reduced sensitivity to increased CO_2 has been revealed. In the primary form a lesion of the medullary chemoreceptors is postulated, while brainstem lesions after infarction, trauma or infection are found in secondary forms.
Chronic obstructive pulmonary disease (COPD), is characterised by a chronic impairment of airflow through the respiratory tract to the lung. Difficulty initiating sleep, frequent awakenings with feelings of respiratory distress and shortness of breath or nocturnal cough are frequently encountered. Oxygen desaturation is more profound during REM sleep. The presence of both OSAS and COPD is referred to as *overlap syndrome.*
Sleep related asthma refers to asthma attacks during sleep. Patients awaken with feelings of dyspnea and wheezing. Mild nocturnal hypoxemia is usually present.
Obstructive sleep apnea syndrome and the more recently described *upper airway resistance syndrome* are discussed in detail below.
It can be very difficult to differentiate between these sleep related breathing disorders and OSAS can coincide with all of the disorders mentioned above.

1.3 The Obstructive Sleep Apnea Syndrome

Obstructive sleep apnea syndrome is characterised by repetitive obstruction of the upper airway during sleep, causing obstructive apneas leading to oxygen desaturations and fragmentation of nocturnal sleep. Snoring, excessive daytime sleepiness, cognitive deficits and sexual dysfunction are associated frequently (7).

1.4 Prevalence of Obstructive Sleep Apnea Syndrome

The prevalence of sleep related breathing disorders and OSAS was investigated more systematically in the late seventies and early eighties, but it already was the most common diagnosis among patients referred to sleep laboratories in the United States before that time (7,10). Interpretation of the data published since, is complicated by differences in study design. The most important difference between studies was one of methodology. Most investigators selected patients with sleep related complaints from a population for polygraphic recording, while others performed polysomnography in unselected cohorts. The latter are likely to provide higher prevalence data, since polygraphic evidence of sleep related breathing disorders may be present in persons without complaints. Comparison of data is further complicated by differences in the definition of OSAS. Not only the number of sleep related respiratory events, but also the nature of these events (apnea-index, apnea/hypopnea-index, sleep-related-breathing-disorder-index, desaturation-index) were defined inconsistently, while the presence of daytime sleepiness was not always included in the definition. Part of the differences in definition of OSAS may be explained by the different recording techniques used to evaluate nocturnal breathing. Table 1.1 summarises the most important publications, concerning the prevalence of OSAS in the middle aged population. If the data in the different studies were sufficiently detailed to allow recalculation of prevalence, defined as Apnea-Hypopnea-Index (AHI) or Desaturation-Index (DI) of at least five per hour of sleep and the presence of daytime sleepiness, this is displayed in the last column.

Table 1.1.

Author and Year	Methodology	Definition of OSAS	prevalence 1	prevalence 2
Lavie 1983	Polysomnography in 72 men, selected by questionnnaire from n = 1502	AHI ≥ 10	0.9%	
Peter 1985	Polysomnography in 20 of 72 male workers (A) selected by questionnaire from n= 354 (B)	50 apneas ≥ 10 seconds or 30 apneas ≥ 20 seconds	40% in A 18% in B	
Peter 1986	Portable recording (ECG, SaO_2) in 72 male patients (A) and 68 unselected technicians (B)	AI ≥ 10	12.5 % in A 10 % in B	
Gislason 1988	Polysomnography in 156 men with snoring and sleepiness from n = 4064	≥ 30 apneas/hypopneas per night	1.3%	1.4%
Cirignotta 1989	Polysomnography in 40 men selelected by questionnaire from n = 3470	AHI ≥ 10	2.7%	4%
Hida 1993	Flow, sound ,and ECG in 159 unselected workers from one company	≥ 30 apneas per night	16.9%	
Bearpark 1993	MESAM-4 in 294 male volunteers and 106 snoring women (Busselton cohort n = 1568)	> 1/3 of the night with snoring and desats ≥ 4%	8.5% men 4.7% women	
Young 1993	Polysomnography in 602 volunteers after questionnaire in n = 3513	AHI ≥ 5 and sleepiness	4% men 2% women	4% men 2% women
Gislason 1993	Polysomnography in 35 women with snoring sleepiness, selected by questionnaire n = 4753	> 30 apneas/hypopneas per night	2.5% women	
Bearpark 1995	MESAM-4 in 294 men selected by questionnaire n = 759	DI ≥ 5 and sleepiness	≥ 3%	≥ 3%

A summary of authoritative publications adressing the prevalence of OSAS. The first column gives the leading author and year of publication. The second column gives a short description of study design and patient selection. The third column gives the authors' definition of OSAS. The fourth (prevalence 1) column the prevalence as estimated by the authors (based on their own definition), the last column (prevalence 2) the prevalence of OSAS as re-estimated following the definition used in this thesis (if presented data were detailed enough to allow re-calculation).

The field survey by Lavie et al in 1983, was conducted on a presumably healthy working population required to be alert (11). As the authors already suggested, this may eliminate the most severe sleep apnea patients, whose excessive daytime sleepiness prevents them from working, resulting in an underestimation of real prevalence. Peter et al in 1985, reported an extremely high prevalence of

sleep related breathing disturbance in selected blue-collar workers with mild coronary risk factors and reported disturbances in sleep-wake-cycle (12). In 1986 the same investigators demonstrated again a high prevalence in subjects with cardiovascular complaints, but they also showed a much lower prevalence in presumably healthy subjects (13). Gislason et al were the first to systematically select subjects at risk for sleep related breathing, by using a complaint specific questionnaire informing about snoring and daytime sleepiness (14). They did not yet incorporate the presence of daytime sleepiness in the definition of sleep apnea syndrome, but their data were based on selection of subjects with daytime sleepiness and reflected the prevalence of OSAS, as defined in this thesis. Cirignotta et al in 1989 also used a questionnaire and a telephonic survey to select patients for recording, and found an intermediate prevalence rate (15). Hida et al defined OSAS purely on nocturnal respiration parameters and reported a high prevalence (16). Young et al were the first to present data on the prevalence of OSAS defined as Apnea/Hypopnea-Index (AHI) ≥ 5 and the presence of daytime sleepiness (17). They showed that approximately 4% of middle-aged men and 2% of middle-aged women meet the minimal criteria for sleep apnea syndrome. These results were confirmed by the works of Gislason in 1993 and Bearpark in 1995, demonstrating again that sleep apnea defined as AHI ≥ 5 and the presence of sleepiness is close to 2.5% in women and at least 3% in men (18,19). Despite the methodological differences between the studies presented, we may safely conclude that the prevalence of OSAS in middle-aged men and women is at least 3% and 2% respectively. In 1996 Knuistingh Neven found in a selected male population of 35 years and older with daytime complaints suggestive for OSAS, a prevalence of 1.7% for SRBD, and 0.45% for OSAS (desaturations and daytime complaints) (20). He correctly stated that the selection of patients by questionnaire and thermistor-recording, before performing polysomnography might have underestimated real prevalence.

Recent epidemiologic data suggest that more than 25% of "healthy" persons older than 65 years have more than 5 apneas per hour of sleep (21,22). This does not mean that these have sleep apnea syndrome, because daytime sleepiness may not be present at all (23). Ancoli-Israël et al found criteria for sleep apnea (AI ≥ 5) in 18% of their randomly selected volunteers, but they demonstrated that, although sleep apnea is widespread in the elderly, it tends not to be manifested in sleep-wake complaints (24). Since the relation between OSAS and cardiovascular disease in the elderly has not been elucidated, the clinical relevance of these data is unclear.

An extremely high prevalence of OSAS in relatively obese commercial truck drivers was shown by Stoohs et al (25). Seventy-nine percent of their subjects had more than five desaturations per hour, while 38% complained of daytime somnolence. These data are alarming, because the relation between sleep apnea and traffic accidents is well established (26,27).

1.5 Pathogenesis

A long history of progressive and excessive snoring almost allways preceedes the diagnosis of OSAS in the individual patient. Snoring is the sound generated by the vibration of the soft parts of the oropharyngeal walls, caused by transmission of a part of the energy of the inspiratory airflow and reflects an increase in upper airway resistance. It is therefore generally accepted that the continuum from habitual snoring to OSAS is caused by the same mechanisms influencing upper airway patency (28).
Certain specific anatomical abnormalities are related with the occurrence of obstruction of the upper airway and may result in OSAS. Micrognathia (Pierre Robin syndrome), macroglossia (acromegaly, Downs syndrome) and hypertrophy of tonsillar and adenoid tissue (frequently encountered in chidren) are only a few of the documented causes (8). The "idiopathic" or "primary" obstructive sleep apnea syndrome is the result of sleep related changes in respiratory control and compliance of the tissue of the upper airway, further enhanced by anatomical properties predisposing to narrowing or collaps of the upper airway during inspiration (29).
In normal sleep we distinguish four stages of NREM sleep, characterised by progressively slower EEG activity and REM sleep characterised by low voltage EEG activity and periods of rapid eye movements (REM). NREM stages I and II are considered as "superficial" sleep. The breathing in NREM I and II is irregular, but with a regular waxing and waning of breathing amplitude. This phenomena is called *periodic breathing*. NREM I and II are therfore considered as unsteady sleep in perspective of respiratory contol (30). During wakefulness breathing is responsive to metabolic stimuli (CO_2, O_2 and pH), but two other influences on breathing can be identified. The degree of wakefulness has a stimulatory effect on breathing, acting through the metabolic control system (31). This influence is described as "state dependent". Activities as phonation demand specific breathing control, which is largely influenced by the cerebral cortex. This influence is described as "behavioural" (31). During NREM sleep, the ventilatory respons to increased pCO_2 is relatively slow compared to wakefulness. The set-point for ventilatory respons to increased pCO_2 seems to be 3 – 7 mmHg higher than during wakefulness. This means that the respiratory control during sleep is less sensitive to increased CO_2. During NREM I and II sleep respiration is controlled by metabolic and state dependent mechanisms, both with a different pCO_2 set-point. Due to the physiologic properties of NREM I in particular, but of NREM II as well, fluctuations between metabolic and state dependent control exist. This means that respiratory control fluctuates between two CO_2 set-points, resulting in periodic breathing that is considered an important condition for the development of OSAS (31-39).
The state dependent decrease in cortical activity decreases the nonautomatic dilatation of the upper airway during sleep (40). The tonic-arousal dilatation of

the upper airway is also decreased due to deactivation of the reticular system. The absence of nonautomatic and automatic dilatations leads to narrowing of the upper airway, which can become occluded if other factors are present. The upper airway collapses due to the negative intraluminal force resulting from the negative intrathoracic pressure during inspiration, resulting in obstructive apnea. Subsequently hypoxia, hypercapnia and increased inspiratory muscular activity induce arousal and the upper airway is opened again (34,35,40,41). With arousal the CO_2 set-point of respiratory control is shifted upwards as a result of increase in cortical activity. Ventilation is increased, until a change in state dependent control with falling asleep decreases the set-point again, and also decreases ventilation and dilatation of the upper airway again. The cycle repeats. These mechanisms contributes to periodic breathing, causing a vicious circle, further enhancing the instabilities in the respiratory control system (35,42).

The size of the pharyngeal lumen depends therefore on the balance between the dilating forces of the upper airway musculature and the narrowing force of the subatmospheric pressure in the upper airway during inspiration. This is the *Balance of pressures principle* as described by Remmers et al. (29) who impliment all the above mentioned principles in a comprehensive model (43).

The musculus (m) tensor veli palatini, m. genioglossus, m. geniohyoideus and the m. sternohyoideus are the most important muscles for maintaining an open upper airway aperture during inspiration (44). As stated above the muscle tone is decreased during sleep, increasing the upper airway compliance to changes in intrathoracic pressure (45). There is evidence that the tone of these muscles is lower in OSAS patients than in controls during sleep. Some investigators found that the upper airway of OSAS-patients is indeed more compliant with increase in negative inspiratory pressures and collapses easier than those of controls (46-50).

The muscles responsible for maintaining an open pharyngeal airway seem to be influenced by changes in lung volume as well. Hoffstein showed that in obese patients with OSAS a considerable variation in pharyngeal cross sectional area occurred with changes in lung volume (51). These results were reproduced later in obese females with OSAS, but it was also demonstrated that the reduction in pharyngeal cross-sectional area between FRC and RV was significantly greater in OSAS patients compared to controls (52,53). Factors related to the lung volume related compliance of the upper airway have not been precisely determined. A reflex activation of the pharyngeal dilator muscles via pulmonairy stretch receptors is postulated. Since lung volume decreases in the supine position, even more so in the presence of redundant abdominal fat these mechanisms partly explain why OSAS occurs at night and why it is usually more pronounced in obese patients (54).

Apart from these neuromuscular and ventilatory control related mechanisms, some anatomical aspects of the upper airway are different between patients with

idiopathic OSAS and normal subjects. Cephalometric analysis in OSAS patients showed that the hyoid bone is positioned more inferiorly, the mandibule is shorter or posteriorly rotated (resulting in micrognathia or retroposition of the mandibula with mandibular deficiency), the space behind the tongue is smaller (posterior airway space or PAS), and the dimensions of the soft palate are larger (55-62). Computerised tomographic studies also demonstrated that the pharyngeal size in OSAS patients was smaller (63-65). One study showed that the reduction of pharyngeal diameter was caused by soft tissue and not by localised deposition of fat (63). A Magnetic Resonance Imaging based study demonstrated that the pharyngeal space of snorers and OSAS patients had a circular or elliptic orientation with the long axis in the sagittal plane (66). The pharyngeal area of normal controls was also elliptic but with the long axis orientated in the coronal plane. The pharyngeal volume in OSAS patients may be further reduced by erythema or edema as a result of vibration trauma caused by repetitive snoring (67).

The soft palate is the most common site of narrowing at the level of the nasopharynx in approximately 80% of patients. Posterior displacement of the base of the tongue and the uvula causes narrowing at the level of the oropharynx in approximately 40% of patients. Narrowing of the hypopharynx is relatively rare in OSAS patients and is achieved by posterior displacement of the epiglottis or by a floppy epiglottis (43,68-74). One in three patients have obstruction at two or more levels (68).

OSAS becomes more pronounced with increasing age. Several mechanisms seem to be responsible. As life progresses there is an increasing number of nocturnal awakenings and the amount of NREM I sleep increases (5). As stated earlier this makes the ventilatory control during sleep more unstable and promotes periodic breathing and repetitive narrowing of the upper airway (31). White showed that upper airway resistance increases with age in men, he was however not able to find a relationship in women (75). With increasing age people tend to gain weight, and the mechanisms discussed below may therefore also contribute to the correlation between age and OSAS. Bliwise illustrated that even in middle-aged and elderly humans in good health an increase in sleep related breathing occurred with age (76). The relation between obesity and OSAS is indisputable, but the mechanism has not been precised (75,77-79). Although it has been postulated that local fat deposits in the pharyngeal wall contributed to upper airway narrowing (80,81), other studies presented contradictory results (63). In the supine position abdominal deposited fat forces the diaphragm upwards and reduces lung volume, resulting in a reduction in cross-sectional pharyngeal volume and increasing upper aiway resistance (51). The strong relation between obesity and OSAS severity is further confirmed by the effect of weight reduction on respiratory parameters (82). Schwartz demonstrated also that upper airway collapsibility decreased after weight loss in OSAS patients (78). A relation between hormonal status and OSAS is

suggested by its predominance in the male patient and by its presence in relation to testosterone and steroid treatment (83,84). Guilleminault demonstrated also that respiratory disturbance was lower in postmenopausal women with OSAS, compared to premenopausal women with OSAS (85). Differences in distribution of fatty tissue between the sexes might however be another plausible explanation.

1.6 Symptoms and Natural History

Snoring is the most frequent symptom in obstructive breathing during sleep. Snoring is a very common phenomenon affecting about 20% of the 30- to 35-year-old population, while by age 60, 60% of men and 40% of women will snore habitually (86). With very few exceptions, all OSAS patients have loud pharyngeal snoring associated with snorting and apneic periods (7,87). The periods of silence are a frequent cause for alarm by the bed partner who may repeatedly try to arouse the patient to make him breath again. OSAS patients are however often unresponsive, even to painful stimuli, and may be disorientated when finally aroused (7). Daytime hypersomnolence is the usual reason for adult patients to seek medical attention (7), but it is our experience that impairment of daytime functioning due to daytime sleepiness may remain unrecognised for many years. Other complaints frequently encountered in OSAS are: difficulties maintaining sleep caused by apneas, abnormal movements during sleep and nocturnal enuresis; morning headache, cognitive deficits and sexual dysfunction (87). Symptoms of OSAS can result in serious problems in personal and professional surroundings. Quality of life can be severely affected as well.

Daytime sleepiness is caused by decreased recuperative effect of nocturnal sleep. Every obstructive apnea or hypopnea is terminated by an arousal resulting from augmented muscle activity during increased inspiratory load, causing fragmentation of nocturnal sleep (88). Sleep fragmentation is indeed demonstrated to be an important determinant of daytime sleepiness (85,89,90). Some investigators found a relation between the amount of nocturnal oxygen desaturation and excessive daytime sleepiness (91,92). In a general population based study, obesity, respiratory symptoms (cough or wheeze), gender and age were found to be related to daytime sleepiness, suggesting that other factors may be complementary to sleep fragmentation and nocturnal hypoxemia in the development of daytime sleepiness in OSAS (93).

The clinical course of OSAS is rather typical. In a sample of 50 patients studied by Kales, 40 patients snored prior to any other symptom, 36 patients had EDS at the onset of their illness (87). Other symptoms came later, but in 50% obesity and hypertension preceeded the complaints for at least one year (87). Martikainen in 1994 followed a relatively random sample of 626 responders to a

questionnaire send to 1600 people and found that snoring indeed increased with age, as did daytime sleepiness (94). These data indicate again that a continuum exists from snoring to OSAS, and that the number and severity of symptoms increase with age and severity of the syndrome (86,87,94). Guilleminault was the first to state that an increase in upper airway resistance may lead from habitual snoring *to upper airway resistance syndrome (UARS)* and to OSAS respectively (95). UARS is characterised by habitual snoring and all the other complaints of OSAS, but without the presence of obstructive apneas to define OSAS (95).

There is epidemiologic evidence that OSAS and *hypertension* are associated, but the criteria for a causal relation have not been satisfied. Some investigators found that snoring was an independent risk factor for hypertension (86,96,97). Others found that snoring was strongly correlated to other clinical findings in apnea patients. Koskenvuo showed a strong association of snoring with smoking, obesity, physical inactivity, hostility and morning tiredness (98). Snoring was not an independent predictor of hypertension in the presence of age, obesity, and alcohol consumption in a study by Stradling (99). A multivariate regression analysis by Hoffstein including 1415 persons showed that snoring was not a significant determinant of blood pressure (100). Snoring may thus not be a direct risk factor for hypertension, but may influence blood pressure via its association with obesity, obstructive sleep apnea and nocturnal desaturation (101). Approximately 30% of patients with primary hypertension are found to have OSAS, while half or more patients with OSAS are found to be hypertensive (11,102-104). Again age, weight, smoking, alcohol abuse and other factors are reported as coinciding factors (104,105).

A relation between snoring and *angina pectoris* was found in men aged 40 – 69 years (97). The same investigators found that frequent to habitual snorers had a relative risk of 1.7 for ischemic heart disease and 2.08 for *ischemic heart disease* and *stroke* combined (106). Coronary artery disease had been diagnosed in 33 of 198 OSAS patients of whom 16 had a previous myocardial infarction and 14 a stroke (107). In 1990 Hung demonstrated that an apnea index (AI) > 5.3 was in independent predictor for myocardial infarction, after adjustment for age, body mass index, hypertension, smoking, and cholesterol levels (108). The relation between snoring or OSAS and stroke has been reported in a small number of studies. After comparing 50 patients admitted for stroke and 100 patients admitted for other disorders Partinen found that the risk ratio for cerebral infarction between snorers and non-snorers was 10.3 (95% confidence limits 3.5 – 30.1), even after correction for age and body mass index (107). Palomaki studied 177 consecutive patients with ischemic stroke and found an odds ratio for snoring and cerebral infarction of 2.13 and an odds ratio for a history of OSAS of 8.00 (109). After excluding apnea, obesity and EDS, the relation between snoring and stroke disappeared. All epidemiologic data suggest a relationship between snoring and especially OSAS and cardiovascular

morbidity, but the presence of confounding factors that are so typical of OSAS render the interpretation rather difficult (98,110,111).
He et al. found that patients with AI>20 had a probability of cumulative eight year survival of 0.63 ± 0.17 versus 0.96 ± 0.02 in case of AI < 20 (112). They analysed 385 male patients. Bliwise estimated a mortality ratio of a RDI>10 to be 2.7, but cardiovascular death was clearly associated with age in this cohort (113). Partinen studied 71 tracheostomised patients and 127 conservatively treated patients (weight loss) and found an age-standardised vascular mortality rate of 5.9 per 100 patients per 5 years in the conservatively treated patients versus a mortality rate of 0.0 in the operated patients (56). Gonzales-Rothi in a retrospective study in 1988 found no statistically significant difference in mortality between OSAS-patients and controls (114). Of the 91 patients 9 died compared to 4 of 35 controls over a relatively short follow-up period of 4-8 years.
Based on the described evidence one may postulate that OSAS could be considered a major public health problem (3). A review by Wright et al however demonstrates that most evidence associating OSAS with cardiac arrhytmias, ischemic heart disease, cardiac failure, systemic or pulmonary hypertension and stroke is inconclusive, because most studies were poorly designed, contained confounding factors or were based on small numbers of subjects (115). Although this is true for most studies, their conclusion that the relevance of sleep apnea to public health has been exaggerated can not be supported by the same inconclusive evidence. The conclusion must be that we indeed need long term population based prospective studies to examine the association between OSAS and morbidity and mortality (4).

1.7 Diagnosis

Due to the complex symptomatology and fast changing insights in the different aspects of OSAS, diagnosis and treatment require expert attention of different clinical specialities (116). A multi-disciplinary approach including a neurologist, otolaryngologist, pulmonologist, and if indicated a maxillofacial surgeon, cardiologist or psychologist with experience in the field of OSAS is important. In the Netherlands a work-group is preparing a consensus based on internationally accepted criteria, stating that diagnosis and treatment of OSAS should be reserved for sleep centres or sleep apnea centres. Each centre must have an experienced multidisciplinary team and possibilities to perform and interpret polygraphic or polysomnographic recordings.
Snoring and daytime sleepiness are the core symptoms of OSAS, but the diagnostic value of these symptoms and other clinical features is very low (117). The medical history remains however very important because it provides information on the impact of daytime complaints in the individual patient and

may give clues for considering OSAS related morbidity or other sleep related disturbances. Different questionnaires for the evaluation of daytime sleepiness and other OSAS related symptoms and comorbidity have been developed (118-120). The additive value of these questionnaires to a brief but adequate history taking is however very small (121).

A physical examination may not contribute much to an adequate diagnosis of OSAS either (117), but it may reveal symptoms of cardio-vascular comorbidity or anatomical abnormalities possibly contributing or causative to OSAS. An adequate physical examination must contain: body weight and length, neck circumference, inspection of nose, mouth and pharynx, blood pressure, pulse, pulmonary and cardial auscultation; peripheral arterial pulsations and inspection for gross anatomical abnormalities of face and thorax (122,123).

Visualisation of the upper airway is important, because it may reveal causative abnormalities (large tongue, tonsillar hypertrophy etc.), and provide evidence of upper airway collapse that may need corrective surgical intervention. The methods that appear most clinically useful to better define pharyngeal narrowing are fiberoptic endoscopy (with or without Mueller manoeuvre) and lateral cephalometry (124). Fiberoptic endoscopy with Mueller manoeuvre must be performed by an experienced oto-rhino-laryngologist. The Mueller manoeuvre is used to define the level and the degree of upper airway obstruction at the nasopharynx and oropharynx, by comparing the inward motion of the pharyngeal wall during vigorous inhalation against occluded nostrils, with the position of the pharyngeal wall in rest (125). Endoscopic examination of the upper-airway during propofol or midazolam induced sleep, commonly referred to as sleep-endoscopy, is probably more reliable in assessing upper airway collapsibility than examination during wakefulness (126). Lateral roengenography of the cranium followed by standardised measurements of the upper airway anatomy is called cephalometry or X-cephalometry (55). This procedure has defined several anatomical differences between normals and OSAS patients, but its predictive value in individual patients undergoing surgery is limited (55,56,59,60,124). Computerised Tomography, Magnetic Resonance Imaging, and other techniques to define upper airway anatomy and collapsibility have been described (65,72,73,127-129). These techniques have been used mainly for research purposes and their clinical value needs further elucidation.

OSAS can not be diagnosed without recording of breathing pattern during sleep (130,131). The gold standard for a definitive diagnosis of OSAS is polysomnography (PSG) (131). A PSG must provide reliable data to enable sleep staging and the scoring of arousals, and to differentiate between obstructive and central apneas. PSG for evaluating sleep-related breathing disorders requires the following channels: EEG, EOG, chin EMG, airflow, arterial oxygen saturation, respiratory effort and ECG or heart rate (131,132). The European consensus is somewhat more pragmatic and advises to record

enough parameters to analyse sleep architecture, sleeping position, respiratory adequacy and respiratory effort. (116). PSG is an expensive and time consuming procedure, and although PSG can be performed at home, most patients will have to be admitted to hospital for at least one night. Based on these restrictions other recording strategies and modalities have been developed. Daytime PSG, split-night recording and siësta recordings have been reported, but these procedures remain unreliable (130). The use of portable recording devices has rapidly increased. This equipment has not been standardised in terms of the type and number of parameters needed for adequate screening for, or diagnosing of OSAS (133,134). The use of portable recordings can lead to inadequate diagnosis and as a consequence improper treatment. Following the American Sleep Disorders Association, the minimal requirement for a portable device are: recording of ventilation, ECG or heart rate and oxygen saturation (133,134). Although studies comparing portable devices to standard PSG are few, portable devices can be useful in diagnosing OSAS in patients with a high pretest probability of OSAS based on clinical features, but in case of a negative test outcome, PSG is indicated (133,134). Portable devices must record unprocessed data and interpretation of the test result must be in the hand of an experienced physician (130,133). In case co-inciding or other sleep related disturbancies are suspected to be present, PSG is still the method of choice for further evaluation of sleep, body movements and breathing pattern (130).
The Multiple Sleep Latency Test (MSLT) is not routinely indicated in the clinical evaluation of OSAS, although it may provide an objective measure of daytime sleepiness (131,135). If more than one sleep disorder is suspected, particulary in case of narcolepsy, MSLT may be indicated (135,136).
Still no definite and internationally accepted definition of OSAS has been reported. The Dutch consensus proposes a combination of polysomnographic and clinical criteria. OSAS is present if a polysomnographic recording shows more than 10 apneas per hour sleep (AI $\geq$ 10) or more than 15 apneas and hypopneas per hour sleep (AHI $\geq$ 15) in the presence of daytime sleepiness. In this thesis we use a different criterion, allowing evaluation of treatment outcome by polygraphy with oxygen saturation trace obtained by a pulse oxymeter. We define OSAS as the presence of more than 5 oxygen desaturations exceeding 3% from base-line per hour sleep and the presence of daytime sleepiness.

1.8 Treatment

1.8.1 General Considerations

The research based evidence for the burden of OSAS on public health and the association with mortality and morbidity may be inconclusive, treatment of sleep disordered breathing in the individual patient may however be very rewarding, althought sometimes difficult (3,4,115,137).
A single treatment modality can not adress the whole spectrum of anatomic, physiologic and independent risk-factors contributing to the development of OSAS in every individual patient. If anatomical or functional abnormalities of the upper airways are found (septal deviation, nasal congestion, large adenoid and tonsils etc), specific treatment is required (138). Surgical and conservative treatment should however allways be combined with general measures concerning the lifestyle of OSAS patients (138-140). Patients must be advised about the effects of smoking, alcohol and sleep medication on sleep architecture and body weight. Abstinence from alcohol before bedtime is an important part of therapy (138). Sleep position training may be an appropriate treatment in patients who have position-related obstruction. Cartwright demonstrated a significant reduction of apneic events in the lateral decubitus position compared to the supine position in ten patients (141). Sleep position training can be accomplished by placing a tennis ball in the back of the patients sleeping garment, preventing him from rolling over to his back (140). Peiser reported a dramatic reduction in sleep apnea index and daytime complaints in 15 patients with OSAS, selected from a larger population scheduled for gastric bypass surgery (82). Schwartz found a significant decrease in upper airway collapsibility and sleep disordered breathing after weight loss (78). Browman followed one patient over three years and found that sleep apnea severity parallelled any increase in body weight (77). Although not all patients found weight reduction helpful in the treatment of OSAS and weight loss may be partial and temporary, dietary control of weight is considered extremely important (138,142). Weight reduction surgery should however not be used routinely in the treatment of OSAS. The effect of these general measures on OSAS related symptoms is limited and further medical intervention is often needed.
Before the simultaneous introduction of UPPP and CPAP for the treatment of OSAS, other strategies were tried. Tracheostomy was the first surgical treatment for OSAS. It is very effective because it bypasses all the obstructive sites of the upper airway. The procedure is psychologically not well accepted by patients, but it may still be used as an interim treatment (143).
Progestational agents have been reported to be useful in a small subgroup of patients who are hypercapnic during daytime, but the role of these agents in the

treatment of OSAS has not been defined (140,144,145).
OSAS has severe consequences for driving ability, and the association between traffic accidents and OSAS has been well established (26,27,146). Every patient should be informed of the regulations and legal implications, as soon as the very first consultation (138).

1.8.2 Uvulopalatopharyngoplasty

Palatopharyngoplasty with partial resection of the uvula, now known as uvulopalatopharyngoplasty, was introduced by Ikematsu in 1952. He succesfully treated loud snoring in a 23-year-old Japanese woman. The technique was fully reported in 1964 (147). In 1981 Fujita et al. were the first to report a modified UPPP, for the treatment of OSAS (148). Many variations in surgical technique originated from the earliest reports (149), but they all intend to reduce redundant velopharyngeal tissue to reduce the degree of pharyngeal obstruction that occurs during the apneic period. The procedure consists of resection of the uvula, distal free margin of the soft palate, palatine tonsils (if present), and any excessive pharyngeal tissue. In the early nineties the UPPP was the most common surgical procedure used for the treatment of OSAS (72).
Since the introduction of UPPP for the treatment of OSAS an enormous amount of studies of the effectiveness of this surgical procedure has been reported in the literature (72,124,150,151). Interpretation of the published material is complicated by a number of general limitations of study design (124,151). Recent critical reviews of the available UPPP literature by Sher and Pépin in 1996 revealed methodological and statistical problems (small sample size, patient selection, no well defined end-points etc), different criteria for effectiveness, short follow-up, and different surgical techniques, to name a few (124,151). No prospective randomised study has been performed or published since (151). The meta-analysis by Sher et al showed that UPPP is, at best, effective in treating less than 50% of patients with OSAS (124). In their original report, Fujita et al. already emphasised that although there was a dramatic improvement, UPPP did not eliminate sleep apnea entirely, because only 8/12 patients had an AHI below 20 and 4/12 had an AHI below 10 after surgery (148). A marked inconsistency between the favourable subjective improvement, as rated by different questionnaires or scoring methods for daytime sleepiness and snoring and the limited objective improvement of sleep pattern, breathing pattern or nocturnal saturation by polysomnography or polygraphy has been reported frequently (14,148,152-157). Subjective improvement in these studies has been reported in 70% to 100% of patients, compared to an objective improvement of approximately 50%. The long-term respons after UPPP has been studied sparsely, but there is evidence for a relapse

of symptoms in 2 to 4 years after surgery (158-160).
Pre-operative selection of patients might improve treatment outcome, but different and unvalidated methods for patient selection have been used in the literature (124). Although more sophisticated techniques have been used to visualise the upper airway before surgery, fiberoptic endoscopy with the Mueller manoeuver and lateral cephalometry appear to be most clinically usefull (124). Studies of the Mueller manoeuver showed that patients with predominant collaps at the velo-pharyngeal level were better responders to UPPP than patients with collaps at any other level (125,161,162). Studies of cephalometry showed poor results in patients with a low position of the hyoid bone, and smaller posterior airway space at the level of the tongue (72,163,164). Several studies evaluating the association between sleep apnea severity and outcome after UPPP, found that patients with high apnea index showed poor results (14,165). A high body mass index has repeatedly been associated with poor surgical outcome as well (14,152,159). The ideal patient for UPPP appears to be one with relatively mild OSAS with predominant narrowing of the upper airway at the level of the soft palate and a normal body weight.
The surgical technique is probably also important in determining post operative outcome. Kimmelman et al reported that a more radical excision of pharyngeal tissue may lead to a higher succes rate, without significantly increasing the number or severity of post-operative complications (166). Comparable results were published by Zohar et al (167). Multiple other mechanisms are thought to contribute to failure of UPPP. Most investigators consider persistent collaps in the operated segment or UPPP related complications responsible for low surgical outcome. However, no conclusive data have been presented so far, because most studies made no clear reference to the occurrence of complications (124,151). Life threatening complications have been reported to result after acute post-operative pharyngeal stenosis or hemorrhage (151,168). Minor complications may be: regurgitation of fluids or food due to velo-pharyngeal insufficiency, loss of taste, foreign body sensation, and change in voice quality (151,168,169)]. Most complications are reported to be mild and to resolve within weeks to months. Post-operative pain, sometimes severe was reported by almost all patients.
In 1990 the Laser Assisted Uvulopalatoplasty (LAUP) was introduced for the treatment of snoring and in the years to follow it was also used in the treatment of OSAS (170,171). No prospective randomised trials, comparing UPPP and LAUP have been reported, but the results and complications of LAUP don't seem to be different from UPPP (171).

Recently a new surgical treatment modality has been described, using radiofrequent energy. This radiofrequent coagulation technique results in volumetric reduction of the soft palate by causing fibrosis of the underlying tissue, without damaging the superficial mucosa. The value of this technique for the treatment of OSAS has not been fully assessed, and further research is needed (126).

1.8.3 Continuous Positive Airway Pressure

In 1981 Sullivan reported that continuous positive airway pressure (CPAP) applied through a nose mask completely prevented obstructive apneas during sleep (172). Although only one prospective randomised placebo controlled study has been performed, a substantial number of studies has recognised the value of CPAP and it is considered the treatment of choice for OSAS (115,137,173,174).
Although CPAP is effective in eliminating snoring, it is not indicated for the treatment of simple or habitual snoring, because no clinical study demonstrates the health benefits in these patients (175). CPAP may be effective in eliminating the polysomnographic signs of central sleep apnea, but its effect on clinical symptoms has not been demonstrated adequately either (175).
The effect of CPAP is mediated mainly by pneumatic splinting of the upper airway (176,177), but changes in lung volume, central chemosensitivity, upper airway muscle activity and upper airway configuration have been reported to contribute also (67,176-182). The improvement of daytime sleepiness and alertness has been demonstrated in a large number of studies (183-187). The subjective improvement of EDS is associated with improvement of sleep architecture and sleep latency, but there is insufficient evidence that sleep structure normalises during CPAP therapy (26,185,188-190).
A limited number of studies has been performed to assess improvement of cognitive performance, mood and quality of life. Engleman at al reported an improvement of sleepiness, cognitive performance in a placebo controlled study (187), but others suggest that irreversible ischemic neuronal damage may be responsible for persisting neurobehavioural manifestations (191).
Although an association between OSAS and cardiovascular sequelae is generally accepted, the long-term effectiveness of CPAP on improvement of morbidity, mortality and quality of life has not been assessed adequately yet (4,115,192). A few small and uncontrolled studies found normalisation of hypertension, improvement of left-ventricular function and a decrease in haematocrit (193-196). These changes could however, also be associated with changes in body weight during treatment (197).
Nocturnal breathing and related daytime symptoms are found to improve almost immediately or within several days or weeks, but this effect stops as soon as

CPAP treatment is stopped (181,186,188,198). If treatment is continued however, CPAP remains effective in improving sleep disordered breathing and daytime symptoms (185,199,200). CPAP may therefore not be considered curative. A study in 57 patients revealed indeed that even after long-term treatment no significant change in AHI was found by polygraphic recording during a single night without CPAP (201). The prerequisite for effective treatment of OSAS is therefore a good compliance to CPAP. Sanders in 1986 interviewed 24 patients who possessed their CPAP for 10 ± 8 months, and reported that 17 patients used their CPAP all night (85% of compliance) (139). Because self-reported compliance was believed to be an over-estimation, Krieger and Kurtz used a built-in time counter that measured the time the machine was running (202). They found a mean rate of use of 5.14 ± 0.31 hours per night and an acceptance rate of 90% after a mean follow-up of 232 ± 27 days. Barone Kribbs et al. used an even more sophisticated time counter that measured actual pressure at the mask (203). They included 35 patients with a total CPAP use of 3.743 days. Patients were unaware of the built-in timer. They found that their patients attempted to use CPAP an average of 66 ± 37% of the days monitored, while only 46% used CPAP at least 4 hours on 70% of the days monitored. Only 2 patients (5%) used it at least 7 hours on 70% of the days monitored. The American Thoracic Society in 1994 states that the overall compliance rates may actually approach 50% at best (175). The acceptance rate may be close to 70% (204-206).
From these figures it may be evident that CPAP is a cumbersome treatment and compliance to therapy is very much depending on whether the patient considers its discomfort and side effects in proportion to its benefits. The most consistent factor associated with good compliance is the experienced improvement of daytime sleepiness during CPAP treatment (203,204,207,208). The most frequently reported adverse complaints are mask related (too tight, hurts the ridge of the nose and upper lip, leaves marks on face and hair, too large, leaks etc.) (205,206). CPAP related complications are mostly minor. Local skin irritation, drying of nasal and pharyngeal membranes (±50%), nasal congestion and rhinorrhea (±25%), and eye irritation by air leak (±25%) are the most common (139,175,206,207). Major complications have been described in case reports only and include pneumocephalus, bacterial meningitis and atrial arhythmia (209-211).

1.8.4 Other Surgical Procedures

Because multiple sites of anatomic obstruction have been demonstrated in OSAS, and UPPP adresses the velo-pharyngeal level only, other surgical treatment strategies have been developed. Although these procedures could be indicated and performed individually, they should be part of a stepwise surgical

protocol with the primary goal to cure the patient (212). Powell et al. described a two-phased surgical protocol with individual stages in which a treatment strategy is planned after identifying the regions of obstruction and applying the specific surgical intervention for treatment at that level, using the most conservative procedures first (212). Phase I includes: nasal reconstruction, UPPP, and inferior mandibular sagittal osteotomy with genohyoid advancement. Phase II includes: bimaxillary advancement, subapical mandibular osteotomy, and base of tongue surgery. Their published data strongly suggest that after proper selection of patients the results of this protocol are comparable to CPAP in 65% of patients after phase I, and in 90% of patients after phase II (212-214). They emphasise that re-evaluation between major steps is mandatory to minimise over-operating. No prospective randomised comparative study of these surgical procedures with CPAP has been performed. In the Netherlands there is no experience with a systematic surgical protocol exceeding beyond UPPP.
Before the introduction of UPPP, tracheostomy was the only surgical alternative. Although this intervention is very effective in reducing snoring and upper airway obstruction, it is now performed only if other treatment modalities remain ineffective in patients with severe cardial and pulmonary symptoms (126,215).

1.8.5 Oral Appliances

Oral appliances increase the upper airway aperture by repositioning the mandible, advancing the tongue and changing the palatal and mandibular position or dynamics (216,217). Despite the large variation in design, the clinical effects are remarkably consistent. Snoring was improved and often eliminated in almost all patients, obstructive sleep apnea improved in the majority of patients, but as many as 40% of those treated were left with significantly elevated AHI (216). Oral appliances are indicated for patients with moderate to severe OSAS who are intolerant of or refuse treatment with CPAP or surgery (218). In case of a small oropharynx, any appliance that could enlarge the airway by advancing the tongue, the mandible or both could be usefull (217). If a disproportionally large tongue is found, any device retaining the tongue in an advanced position could be used (217). Oral appliances may aggrevate temporo-mandibular joint disease and may cause dental misalignment. Oral appliances should be fitted by qualified personel only and follow-up care by a dentist is necessary (216-218). Poly(somno)graphic follow-up is mandatory, because any device may worsen OSAS. In the Netherlands the experience with oral appliances is increasing (126).

1.9 Scope of this Thesis

The Obstructive Sleep Apnea Syndrome (OSAS) is characterized by repetitive cessation of flow through the upper airway, caused by obstruction of the upper airway during sleep (*chapter 1*). Snoring and daytime sleepiness are the core symptoms of OSAS, but cognitive deficits, mood disorders and other symptoms have been described. The long term sequelae of repetitive apneas and nocturnal oxygen desaturation have not been fully elucidated yet (4), but the symptoms may have devastating consequences for the lives of those affected. OSAS is not a rare disorder and its prevalence is estimated to be 4% of middle-aged men and 2% of middle-aged women (*chapter 1*) (17-19). In the perspective of its relative high prevalence and the severity of its symptoms, the OSAS must indeed be considered a major public health problem (3) that deserves expert medical attention and treatment. However, without a complete understanding of the pathogenesis and long-term effects on health outcome of sleep related breathing disorders, the development of effective treatment modalities, that are relatively non-invasive and well tolerated will remain difficult, and further research is therefore of paramount importance.

In this thesis we focus on the treatment of OSAS with Uvulo-palato-pharyngoplasty (UPPP) and Continuous Positive Airway Pressure (CPAP), and pathogenic aspects are studied to illustrate the limitations of surgical therapy (*chapter 2*). The main goal of our studies was to assess the treatment outcome after UPPP (*chapter 3 and 4*) and to evaluate whether the treatment of patients with OSAS caused by predominant collapse at the velo-pharyngeal level should be started with UPPP or CPAP (*chapters 5 and 6*).

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CHAPTER 2

Pathogenesis of Obstructive Sleep Apnea Syndrome

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Upper Airway Patency and Nocturnal Desaturation in Habitual Snoring and Obstructive Sleep Apnea:
Pathogenesis of Sleep Related Breathing Disorders

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2.1 Abstract

The pathogenesis of sleep related breathing disorders is complex. Upper airway anatomy and sleep related changes in respiratory and upper airway muscle control are likely to be involved.
Sixty patients, 53 men and 7 women, referred for excessive snoring or suspected sleep apnea syndrome were analysed by polysomnography, Mueller manoeuvre, cephalometric roentgenography and pulmonary function testing, to evaluate the contribution of static and dynamic upper airway obstruction in the pathogenesis of sleep related breathing disorders and OSAS. Desaturation index and maximal desaturation were used in the analysis as indicators of severity of sleep related breathing disorders. Body Mass Index, increased collapsibility at the base of the tongue by Mueller manoeuvre, increased distance between hyoid and mandibular plane, and increased soft palate diameters by cephalometry as well as a decreased peak inspiratory flow by pulmonary function testing, were found to be related to increased oxygen desaturation parameters. In a multivariate analysis the significant obstruction parameters could explain only 37% of the variability of maximum desaturation and 31% of the variability of desaturation index, 63% and 69% respectively must therefore be explained by other mechanisms. We conclude that instability of respiratory and upper airway muscle control, even enhanced by sleep phase related changes is more important in the pathogenesis of sleep related breating disorders than pure anatomic narrowing of the airway.

2.2 Introduction

The spectrum of sleep related breathing disorders ranges from partial airway collapse and increased upper airway resistance, accompanied by snoring and periods of hypopnea, to complete airway obstruction, resulting in the fullblown obstructive sleep apnea syndrome. Until recently the prevalence of obstructive sleep apnea syndrome was estimated at approximately 1-2% of middle- aged adults, but Young et al. showed that 4% of middle aged men and 2% of middle aged women are likely to meet the minimal diagnostic criteria for the sleep apnea syndrome (1-5).
Characteristic of the syndrome is excessive daytime sleepiness as a result of sleep fragmentation, but a variety of symptoms of functional impairment may develop (6). The respiratory disturbances cause oxygen desaturations and increased sympathetic nerve activity, both contributing to cardiovascular morbidity and mortality in apnea patients. Sleep apnea and snoring are associated with hypertension, angina pectoris, myocardial infarction and ischemic brain infarction (7-12).

The pathophysiologic mechanisms leading to sleep related breathing disorders and obstructive apneas are still unknown, but at least two components are likely to contribute: narrowing of the upper airway and instability of respiratory and muscle control. Upper airway patency is not only defined by static anatomical configuration, but also by dynamic changes of the muscles and soft tissue, caused by airflow and complicated reflex mechanisms of the respiratory system. Using cephalometric roentgenography the influence of bony structures and soft tissue on upper airway space can be assessed, but no information on dynamic obstruction can be obtained. Because it is easily performed and ample normative values are at hand, cephalometry remains the method of choice in assessing overall upper airway morphology (13). Although computed tomography and magnetic resonance imaging show more details of the upper airways and may even be performed during sleep like states, they are less routinely used, because they are expensive, time consuming and only limited normative values are at hand (13). By fiberoptic evaluation in combination with the Mueller maneuvre, the presence of upper airway collapse and local anatomical abnormalities can be visualised and scored (13). Pulmonary function testing, especially the variables of a maximally forced inspiratory manoeuvre, reflects the restriction of airflow caused by dynamic narrowing of the upper airway (14).
In comparison to the anatomical factors, the neurological aspects of ventilatory control and upper airway patency are less accessible for direct investigation. In general, however, periodic nocturnal breathing and sleep related changes in chemosensitivity and upper airway muscle tone and respiratory control are suspected to be major contributors to the development of sleep related breathing disorders (15-22).
In this study we follow the hypothesis that both, disturbed respiratory control and altered upper airway patency play a role in the pathogenesis of the sleep apnea syndrome. We evaluated therefore the contribution of both static and dynamic obstruction parameters on the frequency and severity of respiratory disturbances during sleep. The quantitative assessment of the role of upper airway obstruction will enable us to estimate indirectly the role of disturbed respiratory and muscle control in the complex pathogenetic process.

2.3 Materials and Methods

Sixty consecutive patients , 53 men and 7 women, were included in this study. The mean age of the study group was 50.6 years (sd = 10.7, range 19 - 75 years). All of them have been referred to our clinic because of heavy snoring or suspected sleep apnea syndrome. All patients underwent polysomnography, fiberoptic evaluation, including Mueller manoeuvre, pulmonary function studies and cephalometric roentgenography. The Body Mass Index (weight/length^2)

was calculated for every subject. All patients included in the study were free of concommitant disease and no facial anatomical abnormalities were present.

Polysomnography

All patients underwent polysomnographic recording for one night. The polygraphic recording included electroencephalography, electro-oculography and electromyography registration and sleep stages were scored following the international criteria of Rechtschaffen and Kales (23). Respiration was monitored by thermistors to assess oro-nasal flow, by impedance plethysmography to assess respiratory chest and abdominal excursions and by pulse-oxymetry to detect oxygen desaturation. Apneas were divided into central type (no respiratory excursions and no flow), obstructive type (persisting respiratory effort, but no flow), and mixed type.
Obstructive sleep apnea syndrome was defined as the presence of obstructive apneas during at least ten seconds or more leading to 5 desaturations or more per hour of sleep. Periods of at least 3% reduction of oxygen saturation from baseline were included in the calculation of the desaturation index (total desaturations/total sleep time per hour). The desaturation index and the maximal desaturation were used in our final analysis, because these are most reliably identified.

Cephalometric Roentgenography

Lateral cephalometric roentgenograms were obtained using a standardised method, as described by Riley et al (24). No differences in the positioning of the head were likely to occur, as rotation and flexion of the neck were prevented by using a specially designed frame. All roentgenograms were made in the sitting position, during slow inspiration with the mouth closed and the teeth relaxedly put together. All roentgenograms were made between 09.00 am and noon. Cephalometric parameters were scored by a single physician blind to the clinical and polysomnographic results. We used parameters that have been shown to be significantly different in groups of OSAS patients compared to healthy controls (24-32). The parameters included in our analysis were: the minimal posterior airway space at the level of the tongue base (PAS), the distance between the mandibular plane and the most cranio-ventral aspect of the hyoid bone (MPH), the length of the soft palate, being the distance of the posterior nasal spine to the tip of the uvula (SPL) and the diameter of the soft palate taken at the widest point (SPD). All measurements were expressed in millimeters.

Pulmonary Function Testing

Forced inspiratory and expiratory flow-volume curves were obtained using a heated pneumotachometer, which was volume-calibrated before each measurement. Peak inspiratory flow (PIF) and peak expiratory flow (PEF), were used as markers for upper airway obstruction. The maximum values from at least three acceptable manoeuvres were used in the analysis. PIF and PEF were expressed as their absolute values. Regular oscillations on the respiratory curve were considered present or not-present and were judged by eye. None of the patients included in the study showed signs of obstructive pulmonary disease, as defined by the European Respiratory Society (33).

Mueller Manoeuvre

A fiberoptic naso-endoscopic device was used to visualise the upper airway, to determine airway morphology at the level of the soft palate and the tongue base and to exclude local anatomical abnormalities. The Mueller manoeuvre was performed to assess the collapsibility at the level of the soft palate (MSP) and at the level of the tongue base (MTB), using a five points, semi quantitative scale (0=0%, 1=25%, 2=50%, 3=75% and 4=100% of narrowing of airway space). The manoeuvre was performed in the supine position. All examinations were performed by a otorhinolaryngologist, blind to the polysomnographic data.

Statistical Methods

All obstruction parameters and Body Mass Index were dichotomized around their medians in order to allow univariate and multivariate regression analysis. We report the multiple correlation coëfficient r^2 (a measure for assessment of the contribution of the study parameters to the variation in desaturation parameters) and the p- values in univariate regression analysis of each obstruction parameter on desaturation index and maximal desaturation. A multivariate regression analysis of all study parameters was performed on the two desaturation parameters. This was followed by a stepwise (forward and backward) regression analysis. P- values below 0.05 were considered significant.

2.4 Results

Table 2.1 shows the anthropometric data. No significant differences were found between the male and female subgroups, and they were further analysed as one group. Following our criteria; 35 men and 2 women should be considered sleep apnea patients.

Body Mass Index (BMI) was a significant contributing factor to desaturation index (r^2=0.13, p=0.004), while its contribution to maximal desaturation was low and not significant (table 2.2).

Table 2.1. Anthropometric data of the study population

Parameter	Mean	S.D.	Range
Desaturation Index (DI)(n/hour)	13.8	17.7	0 - 79
Maximal Desaturation (MD)(%)	9.3	7.6	0 - 32
Body Mass Index (BMI)(kg/m2)	28.1	4.8	18.3 - 42.7
Mandibular Plane-Hyoïd (MPH)(mm)	22.4	7.5	5.0 - 46.0
Soft Palate Length (SPL)(mm)	38.5	6.5	25.0 - 57.0
Soft Palate Diameter (SPD)(mm)	11.5	1.8	8.0 - 16.0
Posterior Airway Space (PAS)(mm)	11.6	3.5	3.0 - 21.0
Peak Inspiratory Flow (PIF)(l/sec)	7.95	2.07	2.82 - 12.91
Peak Inspiratory Flow (PIF)(l/sec)	10.20	2.44	3.83 - 14.55
Mueller Tongue Base (MTB)(0-4)	0.8	1.1	0 - 4
Mueller Soft Palate (MSP)(0-4)	2.7	1.3	0 - 4

The results of the analysis using the static cephalometric variables are shown in table 2.2. Increased distance of mandibular plane to hyoid (MPH) contributed significantly to both desaturation index (r^2=0.10, p=0.01) and maximal desaturation (r^2=0.08, p=0.03). Soft palate length (SPL) contributed significantly to desaturation index (r^2=0.13, p=0.004), while its contribution to maximal desaturation was far from significant. The soft palate diameter (SPD) contributed significantly to maximal desaturation (r^2=0.09, p=0.02). Posterior airway space (PAS) was not related to either of the desaturation parameters. Although several cephalometric parameters were significantly related to the desaturation parameters as individual parameters, they explained only 8-13% of the variation in desaturation parameters, as indicated by the r-square values.
Of the pulmonary functions tested both peak inspiratory flow (PIF) and peak expiratory flow (PEF) were significant contributing factors to both desaturation parameters, but their impact on desaturation index was very low (r^2=0.07, p=0.04 and r^2=0.08, p=0.03 respectively), while their impact on maximal desaturation was slightly higher (r^2=0.19, p<0.001 and r^2=0.10, p=0.01 respectively). The results are shown in table 2.2.
None of the variables assessed by Mueller manoeuvre was significantly correlated to the desaturation parameters and the contribution to oxygen desaturation was found to be very low. The relation between collapsibility at the tongue base and maximal desaturation was only a trend (r^2=0.07, p=0.05). The results are shown in table 2.2.

Table 2.2.

		Univariate Analysis		Multivariate Analysis (all parameters)		Multivariate Analysis (stepwise)	
	Median	r^2	p	r^2	p	r^2	p
			DESATURATION INDEX				
BMI	27.3	0.13	0.004*	0.42	<0.001*	0.37	<0.001
MPH	22	0.10	0.01*		0.38		
SPL	38	0.13	0.004*		0.01*		0.006*
SPD	12	0.02	0.37		0.38		
PAS	11	0	0.98		0.36		
PIF	7.16	0.07	0.04*		0.67		
PEF	10.56	0.08	0.03*		0.83		
MTB	0	0.02	0.25		0.38		
MSP	3	0.06	0.06		0.83		
			MAXIMAL DESATURATION				
BMI	27.3	0.04	0.11	0.41	0.15	0.31	
MPH	22	0.08	0.03*		0.11		0.04*
SPL	38	0.04	0.12		0.26		
SPD	12	0.09	0.02*		0.28		0.01*
PAS	11	0	0.79		0.25		
PIF	7.16	0.19	<0.001*		0.38		
PEF	10.56	0.10	0.01*		0.62		
MTB	0	0.07	0.05*		0.02*		0.003*
MSP	3	0.01	0.46		0.63		

Univariate and multivariate analysis (including all parameters and the stepwise analysis) of the obstruction parameters and BMI in relation to Desaturation Index (top half) and Maximal Desaturation (bottom half). For abbreviations; see table 2.1.

In the multivariate regression analysis including all obstruction parameters, 42% of the variation in desaturation index and 41% of the variation in maximal desaturation could be explained by all parameters, while only SPL and BMI were significantly related to desaturation index (p=0.01 and p=0.001 respectively) and only MTB seemed to be significantly related to maximal desaturation (p=0.02). In the stepwise regression analysis SPL and BMI

remained significantly related to desaturation index ($p=0.006$ and $p<0.001$ respectively), while SPD, MPH and MTB remained significantly related to maximal desaturation ($p=0.01$, $p=0.04$ and $p=0.003$ respectively). Only 37% of the variability in desaturation index and only 31% of the variability in maximal desaturation could be explained by these factors (table 2.2).

2.5 Discussion

We included patients referred for snoring or suspected obstructive sleep apnea syndrome (OSAS). In the analysis we did not differentiate between patients fullfilling OSAS-criteria and heavily snoring patients, because we intended to study the continuum of this complex pathogenetic process. We did not use the Apnea-Hypopnea-Index (AHI), because the analysis of desaturation parameters not only provides information about the number but also about the severity of respiratory events and the measure of oxygen desaturation is believed to play a major role in causing cardiovascular disease in OSAS-patients (11,34,35). In addition, desaturation parameters are technically more reliably identified, compared to apneas or hypopneas, since measurement artifacts due to motor activity may occur frequently in some patients. It should, however, be noted that desaturations not preceeded by a respiratory event were not included in the analysis.

Our population represents the whole spectrum of sleep related breathing disorders, from severe snoring alone to OSAS. The comparison of the anthropometric data with other studies is therefore difficult, because most studies use selected patient groups of OSAS-patients, heavily snoring patients, or healthy persons (1-5,25-32). The Body Mass Index we found in our study group is intermediate in comparison to those of OSAS patients and heavily snoring patients presented in the afore mentioned studies. The age group is similar and 90% in our study group is male, findings that are consistent with earlier reports (27,30). Recent epidemiologic data show, however, that sleep disordered breathing is only twice as frequent in men than in women. It may be that women do have less complaints, or are less often referred for further clinical evaluation.

The use of cephalometric analysis of the upper airway is widely accepted (13). Although numerous diameters, distances and angles can be measured, we selected those parameters from recent publications, most constantly showing differences in OSAS-patients compared to controls (25-32). Vertical displacement of the hyoid bone, increased dimensions of the soft palate, and decreased posterior airway space are the most consistent findings in relation to sleep disordered breathing. We found increased vertical displacement of the hyoid bone (MPH) to be the most important contributing factor to both desaturation index and maximal desaturation. The hyoid bone is the origin of

the hyoglossal musculature. Vertical downward displacement of this structure pulls the tongue backward, into the hypopharynx. Strelzow et al. showed that an increase in dimensions of the soft palate, length and diameter, are correlated to an increase in Apnea-Hypopnea-Index (25). We found that increased dimensions of the soft palate had indeed a clear influence on desaturation parameters, but the impact on oxygen desaturation was low.

The usefulness of the pulmonary function variables is limited, because PIF and PEF are influenced also by muscle strength and respiratory effort. PIF provides not only information on static, but also on dynamic obstruction during inspiration; this combination may explain why we found PIF to be the strongest predicting factor to maximal oxygen desaturation, while both PIF and PEF contributed significantly to desaturation index and maximal desaturation.

During sleep muscle tone and respiratory control are influenced by sleep phase related changes, resulting in lower muscle tone and lower vital capacities (16). This means that with unchanged upper airway anatomy, the contribution of changes in respiratory control to dynamic narrowing will even be bigger during sleep. The presence or absence of oscillations on the respiratory curve is not related to either of the desaturation parameters.

When interpreting data obtained by the Mueller manoeuvre we are realising its limitations. The Mueller manoeuvre was performed on awake patients, so the results cannot be extrapolated directly to the sleeping situation, since active contraction of the upper airway musculature during the procedure might occur. On the other hand, with this limitation in mind we believe that the Mueller manoeuvre in awake patients is a useful method in comparing overall collapsibility of the upper airway between patients. We found that part of the desaturation parameters were predicted by collapsibility at the base of the tongue.

A striking finding in our study is that anatomy and collapsibility at the level of the tongue base is related to maximal desaturation, rather than to desaturation index. This is in concordance with our hypothesis (36), that increased collapsibility at the level of the tongue base may lead to longer apneas with more desaturation, because more respiratory muscle effort is needed to regain normal breathing. However, we were not able to show a relation between reduced posterior airway space at this level and the desaturation parameters. This suggests that dynamic narrowing, as seen with the Mueller manoeuvre and pulmonary function testing, is more important in causing obstruction than differences in static upper airway anatomy at that level.

We believe to have included in our final analysis, all variables with reproducible relation to sleep related breathing disorders from the literature (25-32). We found that 30-40% of the variation of the desaturation parameters could be explained by obstruction parameters. This means that approximately 60% of the variability of oxygen desaturation parameters in sleep related breathing disorders is not directly explained by obstructive factors. Lugaresi et al. in 1972

presented data, suggesting that oscillations within the central nervous system are likely to be part of the mechanism causing sleep related breathing disorders (15). Phillipson in 1978 was the first to state that during NREM I/II, the carbodioxide "set-point" was elevated by disappearance of the wakefulness stimulus, causing periodic fluctuation between relative hyperventilation and hypoventilation, during the physiologic changes between wake and NREMI/II, so characteristic of superficial sleep (16). Chapman et al. in 1988 showed that increased "loop-gain" in ventilatory control during sleep results in periodic breathing in OSAS patients (17). Longobardo et al. developed a model-based study and demonstrated the interrelationship between periodic breathing and upper airway resistance (18,19). Their results were reproduced by Khoo et al. in 1991 in their model based study (20). The precise mechanism of interaction, however, remains obscure, but the obstructive apneas during sleep were shown to be dependent on the chemosensitive component of neuromuscular control of respiration and upper airway patency. Onal et al. were able to demonstrate that during an obstructive apnea a reduction in electromygraphic activity of both the diaphragm and the genioglossal muscle could be recorded (21). In general, however, upper airway muscle activity is increased in OSAS patients, compared to normal subjects (22). Those findings indicate that oscillating motor output is another possible underlying cause of obstructive apneas.

Our results again stress the complexity of the pathogenetic mechanisms of sleep related breathing disorders and OSAS. Thirty to 40 percent of desaturation parameters may be explained by obsruction parameters alone, 60-70% may be explained by multiple other mechanisms, including; oscillations within the central nervous system, deranged motoneuron activity of the upper airway and respiratory musculature, and changes in metabolic set-point increasing the loop-gain of the respiratory control system during sleep. All of these mechanisms are subject to normal ageing related changes in neuromuscular properties and sleep architecture, making the understanding of the pathogenesis of sleep related breathing disorders even more difficult. We conclude that instability of respiratory and muscle control, even enhanced by sleep phase related changes is more important in the pathogenesis of sleep related breating disorders than is pure anatomic narrowing of the upper airway.

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CHAPTER 3

Short-term Results of Uvulopalatopharyngoplasty for Obstructive Sleep Apnea Syndrome

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Uvulopalatopharyngoplasty for the Obstructive Sleep Apnea Syndrome: Value of Polysomnography, Mueller Manoeuvre and Cephalometry in Predicting Surgical Outcome

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3.1 Abstract

Sixty consecutive patients with obstructive sleep apnea syndrome, 53 men and 7 women were analysed by introspective questionnaire, polysomnography, roentgenographic cephalometry and Mueller manoeuvre before and six months after uvulopalatopharyngo-plasty (UPPP), to assess surgical outcome and the prognostic value of pre-operative evaluation. Seventy three percent reported improvement of snoring and 55% reported improvement of excessive daytime sleepiness. Thirty-five percent showed a decrease of at least 50% in desaturation index, 20% showed an increase of mean saturation, and 29% showed an increase of lowest saturation. Thirteen percent had post-operative desaturation index below 5. Although the improvement of desaturation parameters was marked in some patients, the overall change was not significant. Body Mass Index, nor any of the cephalometric variables were significantly correlated to surgical outcome. Increased difference in collapsibility between soft palate and base of the tongue showed a close to significant relation with improvement of desaturation index. High desaturation index, low mean saturation and deep lowest saturation were found to be slightly predictive of improvement in nocturnal desaturation. It is concluded that UPPP is effective in reducing snoring and daytime sleepiness over a 6 months follow-up period, but that the overall improvement in nocturnal desaturation is limited and difficult to predict. Further research is needed to evaluate long term efficacy of UPPP.

3.2 Introduction

Approximately 3-4% of middle-aged men and 2% of middle-aged women are likely to meet the minimal criteria of obstructive sleep apnea syndrome (OSAS) (1,2). Snoring, excessive daytime sleepiness and nocturnal breathing stops are the cardinal symptoms of OSAS (3), but associated neuropsychological defecits, mood disorders and cardiovascular sequelaea may diminish daytime performance and life expectancy (4-9).
Many surgical and non-surgical techniques have been developed to treat OSAS. Tracheostomy is very effective in improving both snoring and nocturnal desaturations, but its invalidating effects are a serious limitation for routine OSAS treatment (10). Although nasal Continuous Positive Airway Pressure (nCPAP) has been shown to be very effective in improving daytime sleepiness and nocturnal desaturations (11), its burden on sleeping and social behaviour may be responsible for low long term compliance (12). In 1981 Fujita introduced the Uvulopalatopharyngoplasty (UPPP) (13), a procedure developed earlier by Ikematsu for the treatment of snoring (14). UPPP can effectively reduce snoring, daytime sleepiness and nocturnal desaturations, but its surgical outcome is highly variable and difficult to predict. In the absence of simple and

easily acceptable treatment alternatives, careful identification of selection criteria, may enable us to offer UPPP only to those who will benefit most.
The goal of this study is to assess the prognostic value of routine pre-operative evaluation by polysomnography, Mueller manoeuvre, cephalometric roentgenography, Body Mass Index and age to treatment outcome after UPPP. We therefore assessed the effectivity of UPPP in reducing snoring, daytime sleepiness and nocturnal desaturations after a six months follow-up period in a large consecutive series of 60 patients.

Table 3.1.

Parameter	Base-line		Six months		
	Median	95%	Median	95%	n
Age	49	29 - 71			
Body Mass Index	29.6	21.4 - 38.7	28.4	21.0 - 38.8	52
Snoring score	3	1 - 4	1	0 - 4	58
Sleepiness score	3	0 - 5	1	0 - 5	57
Desaturation Index	15	6 - 89	18	0 - 75	43
Base-Line Saturation	95%	90% - 98%	95%	92% - 98%	42
Mean Saturation	91%	77% - 94%	91%	83% - 96%	42
Lowest Saturation	84%	54% - 90%	82%	61% - 96%	43

Anthropometric data, baseline characteristics and six months follow-up data. The second colomn under Base-line and Six months displays the 95 interpercentile range of each variable. The last colomn presents the number of patients in whom pre- and post-operative data are complete.

3.3 Materials and Methods

We included sixty consecutive patients, 53 men and 7 women. All patients have been referred to our clinic because of snoring or daytime sleepiness; polysomnography confirmed the diagnosis of obstructive sleep apnea syndrome (OSAS). Anthropometric data and base-line characteristics are summarized in table 3.1. A specially designed questionnaire with semi-quantitative scales was used to evaluate snoring and daytime sleepiness before and after surgery (see table 3.2).

Table 3.2.

• Scale for severity of Snoring
0 = No snoring or occasional snoring
1 = Every night snoring, but not influencing sleep of partner
2 = Every night snoring, sleeps separated occasionally (≤ 1× / week)
3 = Every night snoring, sleeps separated ≥ 2× / week but ≤ 7× / week
4 = Every night snoring, sleeps separated every night
• Scale for Daytime Sleepiness
0 = No sleepiness
1 = Occasionally fighting against falling asleep
2 = All day fighting against falling asleep
3 = All day fighting and falling asleep on quiet moments
4 = All day fighting and falling asleep during activity
5 = All day fighting and sleeping more than 5 hours during daytime

The semi-quantitative scale for Snoring and Sleepiness (see material and methods).

Improvement of nocturnal desaturation parameters was assessed by polysomnography before and after UPPP. Fiberoptic nasendoscopy with Mueller manoeuvre and cephalometric röntgenography were only performed during pre-surgical evaluation. The Body Mass Index (BMI = kg/m^2) was calculated for every subject. All patients included in the study were free of concomitant disease and no facial anatomical abnormalities were present.

Polysomnography

The polygraphic recording included electroencephalography, electro-oculography and electromyography. Sleep stages were scored following the international criteria of Rechtschaffen and Kales (15). Respiration was monitored by thermistors to assess oro-nasal flow, by impedance plethysmography to assess respiratory chest and abdominal excursions and by pulse-oxymetry to detect oxygen desaturation. Apneas were divided into central type (no respiratory excursions and no flow), obstructive type (persisting respiratory effort, but no flow), and mixed type. Obstructive sleep apnea syndrome was defined as the presence of obstructive apneas during at least ten seconds or more leading to 5 desaturations or more per hour of sleep. Periods of at least 3% reduction of oxygen saturation from baseline were included in the calculation of

the desaturation index (total desaturations/total sleep time per hour). The desaturation index, mean saturation and maximal desaturation were used in our final analysis. The recording was repeated six months after surgery.

Cephalometric Roentgenography

Lateral cephalometric roentgenograms were obtained using a standardised method, as described by Riley et al (16). No differences in the positioning of the head were likely to occur, because rotation and flexion of the neck were prevented by using a specially designed frame. All roentgenograms were made in the sitting position, during slow expiration with the mouth closed and the teeth relaxedly put together. All roentgenograms were made between 09.00 am and noon, to avoid inter-individual differences that may result from absorbtion of pharyngeal oedema. Cephalometric parameters were scored by a single physician blind to the clinical and polysomnographic results. The parameters included in our analysis were: the minimal posterior airway space at the level of the tongue base (PAS), the distance between the mandibular plane and the most cranio-ventral aspect of the hyoid bone (MPH), the length of the soft palate, being the distance of the posterior nasal spine to the tip of the uvula (SPL) and the diameter of the soft palate taken at the widest point (SPD). All measurements were expressed in millimeters.

Mueller Manoeuvre

A fiberoptic naso-endoscopic device was used to visualise the upper airway morphology. The Mueller manoeuvre was performed to assess the collapsibility at the level of the soft palate (MSP) and at the level of the tongue base (MTB), using a five points, semi quantitative scale (0=0%, 1=25%, 2=50%, 3=75% and 4=100% of narrowing of airway space). The manoeuvre was performed in the supine position. The subjects were asked to make a maximal inspiratory effort with the mouth closed and the examiner pinching the nostrils. By carefully releasing the nostrils until a minimal airflow arises, the examiner checks if the inspiratory effort is close to maximal. All examinations were performed by the same otorhinolaryngologist, who was blinded for the polysomnographic data.

Uvulopalatopharyngoplasty (UPPP)

Subjects were positioned as for tonsillectomy. The surgical procedure was performed under general anesthesia with a naso-tracheal intubation. The uvula was pulled towards the surgeon. The resulting natural horizontal crease in the pillar mucosa was used as the line for incision. The oral side of the palatal mucosa and sub-mucosa were removed, expanding laterally if a pre-operative lateral collapse was found. The naso-pharyngeal side of the palatal mucosa and

sub-mucosa were not removed. The uvula itself was shortened, if necessary, but not removed. If present, redundant tonsillar fossa mucosa and tonsillar tissue were also removed. The palatoglossal and palatopharyngeal muscles were spared during the procedure. Finally the posterior pillar was advanced and sutured to the anterior pillar with the suture line away from the nasopharynx.

Statistical Methods

Base line characteristics and post-operative data are presented as median and 95 interpercentile range. Improvement in snoring, daytime sleepiness, nocturnal desaturation parameters and Body Mass Index was analysed with the Wilcoxon matched-pairs signed-ranks test. The relationship between post-operative changes and changes in BMI was analysed by regression analysis. Prognostic value of pre-operative measurements on snoring and sleepiness was assessed by the chi-square test for a 2xr table. All continuous parameters were divided in 4 categories (quartiles) to do so. Prognostic value of pre-operative measurements on nocturnal desaturation was also analyzed by univariate regression analysis, followed by stepwise multi-variate analysis. Body Mass Index, age, soft palate length, soft palate diameter, posterior airway space, distance from mandibular plane to hyoid, collapsibility of soft palate by Mueller manoeuvre, difference between collapsibility between soft palate and tongue base, desaturation index, mean saturation and lowest saturation were included in the analysis. P-values below 0.05 were considered to indicate significance.

3.4 Results

Since no significant differences were found between male and female subgroups, they were analysed together.
Seventy three percent of our population reported improvement of snoring of at least one position on the snoring scale, while 20% reported no change and 7% reported an increase. The improvement of snoring in the group was found to be highly significant ($p = 0.0001$). Fifty five percent reported improvement of at least one position on the daytime sleepiness scale, while no change was reported by 42% percent. This improvement was also found to be highly significant ($p = 0.0001$). Only three percent reported an increase in daytime sleepiness.
Detailed pre- and post-operative polysomnographic data were available in 43 patients. Anthropometric data and baseline characteristics were not significantly different from the remaining 17 patients. No significant improvement in any of the nocturnal desaturation parameters was present. The changes in Desaturation Index (DI) are summarised in table 3.3. In only 8 cases (13%) a post-operative DI below 5 could be recorded. 28 Patients showed a post-operative DI below 20, but only seven of those had a pre-operative DI

above 20. The changes in the other desaturation parameters are summarised in table 3.4. Increase of mean saturation from below 90% to above this level was present in only 8 subjects.

Table 3.3.

Change in Desaturation Index	**≥ -50%**	**≥ -10%**	**< ±10%**	**≥ +10%**
Percentage of patients	35	55	10	35

Change in Desaturation Index (DI). The percentage of the studygroup showing a decrease of at least 50%, a decrease of at least 10%, a change of less than 10% and an increase of at least 10% is displayed respectively. Negativity means improvement.

Table 3.4.

Change in Mean Saturation	**≥ +3%**	**< ±3%**	**≥ -3%**
Percentage of patients	20	53	27
Change in Lowest Saturation	**≥ +5%**	**< ±5%**	**≥ -5%**
Percentage of patients	29	51	20

Changes in Mean Saturation and Lowest Saturation respectively. Positivity means improvement. The cut-off point are rather arbitrary and result from "visual dichotomisation".

In 52 cases the Body Mass Index (BMI) could be assessed reliably both before and after surgery. A significant decrease in BMI was present ($p = 0.001$), 65% showed weight reduction, 13% did not change, and 22% gained weight. Change in BMI was not related to changes in snoring ($p = 0.97$), daytime sleepiness ($p = 0.62$), DI ($p = 0.98$), mean saturation ($p = 0.47$) and lowest saturation ($p = 0.83$). The data obtained by Mueller manoeuvre and cephalometric analysis are summarized in table 3.5 and 3.6.

Table 3.5.

	Soft Palate (SP)	Tongue Base (TB)	Difference (SP-TB)
- 25%			1
0%	0	21	4
25%	1	11	13
50%	9	11	13
75%	21	4	13
100%	19	3	6

The number of patients with collaps of the upper-airway by Mueller manoeuvre at the soft palate and at the tongue base, and the difference between the two levels (semiquantitative scale as defined in text).

Table 3.6.

Soft Palatum Length (n = 46)	42.5 (27.9 - 55.6)
Soft Palatum Diameter (n = 41)	13.0 (8.7 - 18.6)
Distance Mandibular Plane to Hyoid (n = 47)	21.4 (5.7 - 36.9)
Posterior Airway Space (n = 46)	12.7 (4.2 - 32.9)

The parameters of the cephalometric analysis are presented as their median and 95%-interpercentile range (in millimeter).

Body Mass Index, nor age, nor any of the cephalometric measurements was related to any of the post-operative changes. The relation between increased difference in collapsibility between soft palate and tongue basis, and improvement in DI was almost significant ($p = 0.051$) (see fig 3.1). Subjects with higher pre-operative DI showed significantly higher improvement of DI (see fig 3.2). Improvement in mean saturation was significantly correlated to lower pre-operative mean saturation and lowest saturation levels (see fig 3.3 and fig 3.4). Improvement in lowest saturation was significantly correlated to lower mean saturation and lowest saturation levels (see fig 3.5 and fig 3.6).

Figure 3.1.

Relationship between collapsibility index (collapsibility soft palate minus collapsibility tongue base by Mueller manoeuvre) and improvement of desaturation index (desaturation index post-operative minus desaturation index pre-operative; negativity is improvement). Due to unequal distribution of data over de different degrees of collapsibility index, three subgroups had to be formed to allow statistical analysis ($p = 0.05$, $R^2 = 0.10$).

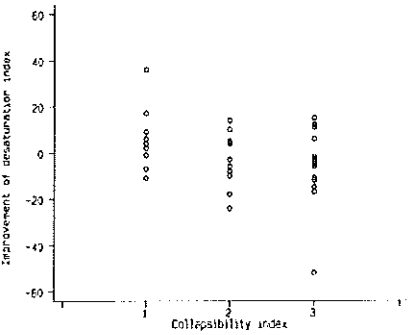


Figure 3.2.

Relationship between pre-operative desaturation index and improvement of desaturation index (desaturation index post-treatment minus desaturation index pre-treatment; negativity is improvement) ($p = 0.01$, $R^2 = 0.15$).

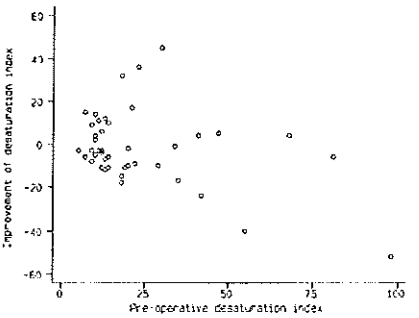


Figure 3.3.

Relationship between mean pre-operative saturation and improvement of mean saturation (mean saturation post-treatment minus mean saturation pre-treatment; positivity is improvement) ($p = 0.001$, $R^2 = 0.24$).

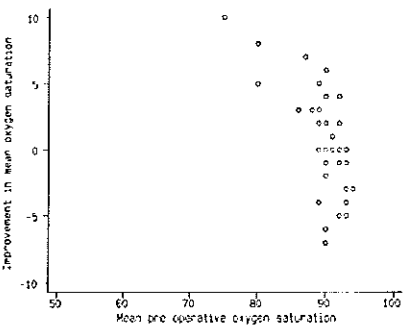


Figure 3.4.

Relationship between lowest pre-operative saturation and improvement of mean saturation (mean saturation post-treatment minus mean saturation pre-treatment; positivity is improvement) ($p = 0.001$, $R^2 = 0.25$).

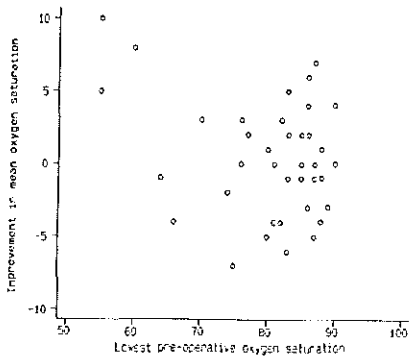


Figure 3.5.

Relationship between mean pre-operative saturation and improvement of lowest saturation (lowest saturation post-treatment minus lowest saturation pre-treatment; positivity is improvement) ($p = 0.0001$, $R^2 = 0.48$).

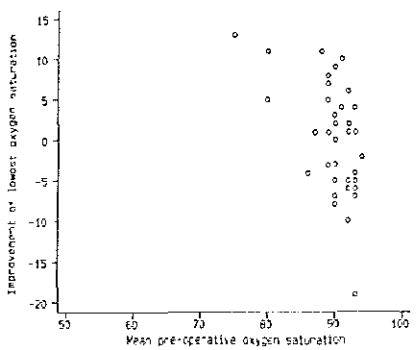
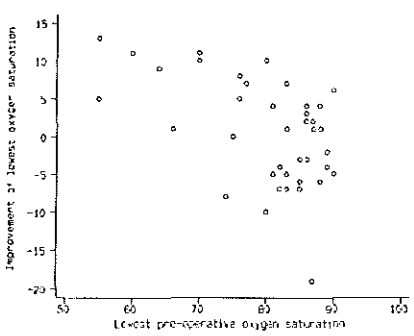


Figure 3.6.

Relationship between lowest pre-operative saturation and improvement of lowest saturation (lowest saturation post-treatment minus lowest saturation pre-treatment; positivity is improvement) ($p = 0.04$, $R^2 = 0.11$).



In the stepwise multivariate analysis no simultaneuos significant predictive factors could be identified.
Post-operative complications were relatively rare. Twelve percent of our patients needed antibiotic treatment for wound infection, 11% reported intolerable pain, regurgitation was found in 3% and rebleeding in 2%. After 6 months, only 7% reported mild speech problems, but did not need further treatment, while only 2% complained of occasional regurgitation of fluids. Ninety-one percent did not experience any long term side effects of the surgical procedure.

3.5 Discussion

We demonstrate again that UPPP is a powerful tool in the treatment of snoring and daytime sleepiness, and our findings confirm those in earlier reports. Prominent reduction in the loudness of snoring was reported by the spouses of all patients presented by Walker et al. (17). Eighty-eight percent of patients reported by Davis et al. marked themselves as improved (18). Both studies present data obtained by subjective judgement of the patient, without any quantification, and may therefore overestimate the real effect. Macnab et al. used a semi-quantitative scale to assess improvement of snoring, and found 76% of their population to be significantly improved (19). Although their post-operative questionnaire contained suggestive questions with more options for improvement than for worsening, their data resemble ours. Assessment of post-operative improvement of snoring expressed in decibels may show different results, but introduces a parameter without clinical relevance. The majority of studies adressing improvement of daytime sleepiness after UPPP, report un-quantified and subjective markings of the patients (18,20-22). Seventy-one percent of 38 patients improved at least 50% on a semi-quantitative sleepiness scale presented by Regestein (23). Although it is impossible to compare two different semi-quantitative scales directly, their data seem to be in concordance with our findings. We used our semi-quantitative scale to assess snoring and daytime sleepiness before and after surgery, and since it is unlikely that patients recall their ratings from 6 months earlier, we believe to have an objective assessment of the improvement of snoring, and daytime sleepiness complaints.
The disparity between improvement of complaints (subjective improvement) and improvement of respiratory parameters (objective improvement) is reported repetitively, and our data are in concordance with these earlier reports.(17,18,20-26) Due to the absence of consensus on the definition of the sleep apnea syndrome, different criteria are used to describe post-operative changes in respiration. Most authors use a combination of apneas, hypopneas and oxygen desaturations, and define apnea-index, apnea-hypopnea-index,

respiratory-distress-index or severity index. We used the desaturation-index (DI), because respiration related desaturations are easy to detect and movement related artifacts can easily be excluded. The improvement of sleep apnea, defined as improvement of respiratory parameters of at least 50%, ranges from 20% to 90%, with a mean respons rate of approximately 50%.(13,17,20-22,24-35). If we define respons as improvement of DI of at least 50%, our respons rate is only 35%. He et al. showed in a retrospective study that mortality was significantly increased in untreated patients when the apnea-index exceeded 20 (7). If this conclusion is valid for DI as well, than this may mean that 47% (28/60) of our patients could be considered sufficiently treated, but only 7 of them had a pre-operative DI above 20. Since we consider OSAS to be present if at least 5 desaturations exceeding 4% from base line per hour are found, only 13% can be considered cured. The use of DI < 5 as a criterion for respons may be more sensible, since Hung et al. found that a AI > 5.3 was an independent predictor of myocardial infarction (8).

The variation in response can be explained by differences in criteria for improvement, differences in surgical technique (36), and differences in patient selection. Many investigators have tried to isolate useful clinical selection criteria for UPPP, but published results have been inconclusive so far.

We did not find BMI to be related to post-operative outcome. This is in concordance with other reports (26,27,33,37), but some authors demonstrated that high weight/BMI correlated to a low respons (22,24,29,31). In contrast to these reports, Fujita et al. found that all non-responders showed a body weight less than 125% of ideal body weight (21). However they did not find that response increased systematically with increase in body weight. These data suggest that patients with high BMI may be unsuitable candidates for UPPP in general, but BMI alone is not sufficient to predict surgical outcome.

As far as we know no data are available on age and surgical outcome. We found that increased age tended to be related to improvement in DI. Age and nocturnal desaturation were not related before surgery, and we believe that this finding may be a coincidence.

Small posterior airway space (PAS) tended to be correlated with improvement of sleepiness and increased distance between mandibula and hyoid (MPH) to improvement of mean saturation, but none of the cephalometric measurements was significantly related to post operative outcome. It is interesting however to notice that especially these two parameters (PAS, MPH) are found to be related to surgical outcome by other authors. Riley demonstrated that good responders had MPH values below 20 millimeter and PAS of at least 10 millimeter, but he did not present a reliable statistical analysis (38). DeBerry-Borowiecki showed that the position of the hyoid bone and the size of the tongue in relation to the oral cavity were highly correlated with the level of succes of UPPP (25). These findings suggest that the position of the hyoid bone, the fulcrum of the hyoglossal musculature and the size of the tongue may indeed be important. A

vertical downward displacement of the hyoid pulls the tongue deeper in the airway and reduces the airway space. This effect is even more pronounced in the presence of a large tongue mass.

The possible role of narrowing of the upper airway at the base of the tongue is further illustrated by the findings of the Mueller manoeuvre. We found that increased difference in collapsibility between the level of the soft palate and the level of the tongue base is related to improvement in desaturation index ($p = 0.05$, $R^2 = 0.10$). Velopharyngeal collaps was shown to be correlated with a good respons (25), and collaps at the tongue base with a negative influence on surgical outcome (39,40). Although the Mueller manoeuvre is performed during wakefulness, it may give us information regarding the differences in potential collapsibility between the region of the soft palate and the region of the tongue base during sleep, and may therefore be useful in pre-operative selection.

The other statistically significant predictive factors we found were high pre-operative desaturation index, low pre-operative mean saturation and low pre-operative lowest saturation. These findings are in accordance with those of Calderelli et al., who showed that UPPP appears to be most effective in patients whose apnea index is above 70 (37). However our data show that although patients with severe nocturnal desaturation are likely to show a decrease in nocturnal desaturation severity of approximately 50%, only a minority of them should be considered cured ($DI < 5$). In contrast many investigators report that patients with light to moderate sleep apnea severity tend to show a better respons than severe sleep apnea patients (24,25,27,29,41), and others report no difference between responders and non-responders (21,26,30,33). The value of respiratory parameters as assessed by polysomnography as predictors of surgical outcome is therefore uncertain, but patients with severe nocturnal desaturation seem to be poor candidates for UPPP, because, although they may show significant respons, they improve insufficiently to be considered cured.

We conclude that UPPP is very effective in reducing snoring and daytime sleepiness in sleep apnea patients, but that the improvement in nocturnal desaturation is poor and impossible to predict in any individual patient. With other treatment modalities to our disposition we must be very selective in proposing surgical treatment for OSAS, but no rational predictive factors are isolated yet. UPPP should maybe be reserved for those patients who refuse or do not respond to other modalities and who preferably show little or mild collaps at the base of the tongue, do not suffer from severe nocturnal desaturation, and are not severely overweight. It is however our experience that quite a number of initial good responders will suffer from sleep apnea again in two to three years after UPPP. No large studies on the long term outcome of UPPP for sleep apnea are available yet, but if this high probability of relapse is true we must show even more reservation in performing UPPP for obstructive sleep apnea.

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CHAPTER 4

Long-term Results of Uvulopalatopharyngoplasty for Obstructive Sleep Apnea Syndrome

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4.1 Abstract

Objectives: Assessment of the long-term effect of uvulopalatopharyngoplasty (UPPP) on snoring, excessive daytime sleepiness (EDS) and nocturnal oxygen desaturation index (ODI) in patients with Obstructive Sleep Apnea Syndrome. *Study Design*: Evaluation of snoring, EDS and ODI in patients treated by UPPP earlier. *Materials and methods*: Patients (n = 58) with a follow-up period of 11 – 74 months (median 34) were included in this study. Snoring and EDS were scored on specially designed semi-quantitative scales. In all patients ODI was calculated from pulse-oximetry combined with polysomnography at base line and by polygraphy (MESAM 4) during follow-up in 38 patients. Long-term response was compared to 6-months response in the same cohort. *Results*: There was a long-term improvement of snoring in 63% of patients, no change in 23%, and a deterioration in 14% ($p < 0.00001$). Overall snoring increased slightly between 6 months and long-term follow-up. There was an improvement of EDS in 38%, no change in 27%, and a deterioration in 35% ($p = 0.80$). EDS showed a relapse to pre-operative levels between 6 months and long-term follow-up. The median improvement of ODI was –1 (95%-interpercentile range –73 to 51) and was not significant ($p = 0.35$). In 5 of 13 patients in whom ODI at baseline exceeded 20, ODI was reduced below 20. In 4 of the 38 patients ODI was reduced below 5. The improvement of ODI decreased significantly between 6 months and long-term follow-up ($p = 0.03$). We found no relation between Body Mass Index, Mueller maneuver, X-cephalometry and long-term outcome. An additional finding was that the ODI decreased after UPPP in combination with tonsillectomy, compared to a slight increase after UPPP alone; the difference was significant ($p = 0.008$). *Conclusion*: The response to UPPP for OSAS decreases progressively over the years following surgery. UPPP in combination with tonsillectomy was more effective than UPPP alone.

4.2 Introduction

Since the introduction of uvulopalatopharyngoplasty (UPPP) for the treatment of sleep apnea syndrome in 1981 (1) the short-term effect of this procedure has been established, but the long-term response has been studied less frequently and remains inconclusive (2-4).

The prevalence of obstructive sleep apnea syndrome (OSAS) is estimated to be 3-4% in middle-aged men and 2% in middle-aged women (5,6). Snoring, excessive daytime sleepiness and nocturnal apneas are the cardinal symptoms of OSAS. These symptoms and other related sequelae may have devastating effects on the lives of those affected. Because of its prevalence and sequelae OSAS should be considered a major public health problem (7).

Many surgical and non-surgical treatment modalities for OSAS have been

described. In comparison to other surgical procedures UPPP is less invasive and relatively well tolerated, but the response rate as defined by different criteria predominantly based on respiratory parameters is approximately 50% or less on short-term follow-up (2,3,8). The long-term effectiveness of UPPP in OSAS has been investigated in a small number of studies with the number of included patients ranging from 15 to 50. Improvement of snoring and daytime sleepiness are assessed on subjective basis without a scaled reference and all studies consider different respiratory parameters to define response (9-13).
Continuous Positive Airway Pressure (CPAP) was also introduced in 1981 (14). Although CPAP has been shown to be effective in improving both daytime sleepiness and nocturnal desaturations and is considered as treatment of first choice (15), its therapeutic use seems to be seriously limited by low long-term compliance (16). Furthermore, the effectiveness of CPAP in improving health outcome has not been assessed reliably in experimental studies, providing no evidence-based standard for indication and clinical follow-up for this treatment modality (17).
Although no clear evidence-based criteria for the indication and patient selection for UPPP exist either, UPPP can not be regarded as ineffective and a small number of patients might indeed be permanently cured after this relatively simple surgical procedure. Therefore it is of paramount importance to more precisely evaluate the long term outcome of UPPP and to identify useful criteria to select patients that are likely to respond well to this surgical procedure (3,4).
In the present study we assessed the effectiveness of UPPP in improving snoring, daytime sleepiness and nocturnal desaturation after long term follow-up. Snoring and daytime sleepiness were scored on a semi-quantitative scale and nocturnal desaturations were obtained by oximetry in combination with polysomnography or a multichannel recording device (MESAM 4). Pre-operative data obtained by the Mueller maneuver, cephalometry, and polysomnography were analyzed to identify possible selection criteria. In addition the contributive effect of tonsillectomy in combination with UPPP compared to UPPP alone was also analyzed. We studied 58 of 60 patients included in an earlier report on the effects of UPPP six months after treatment and evaluated whether early responders proved to be late responders as well (8).

4.3 Materials and Methods

We included 51 men and 7 women of a cohort of 60 patients with OSAS we described in a report on short-term follow-up in 1997 (8). All patients had been referred to our clinic because of snoring or daytime sleepiness, and underwent polysomnographic recording to confirm the diagnosis of OSAS. None of the included subjects used CPAP, was suffering from concomitant disease or had abnormal facial anatomy. All UPPPs were performed between February 1988 and

September 1993. Long-term follow-up ranged from 11 – 74 months with a median of 34 months after surgery. Anthropometric data are listed in Table 4.1.

Table 4.1.

	Baseline	*6 months*	*34 (11-74) months*	
	Median (95%-interpercentile range)	Median (95%-interpercentile range)	Median (95%-interpercentile range)	n
age (years)	49 (29 – 72)			58
BMI	29.6 (21.3 – 38.8)	28.4 (20.9 – 38.9)	28.4 (18.5 – 42.0)	45
Snoring score	3 (1 – 4)	1 (0 – 4)*	2 (0 – 4)*	57
Sleepiness score	3 (0 – 5)	1 (0 – 5)*	3 (0 – 6)	57
Polysomnography at baseline and MESAM after 34 (11 – 74) months				
Desaturation Index	14 (6 – 98)	not available	13 (1 – 87)	38
Response ≥ -50% DI		not available	34%	38
Polysomnography at baseline and 6 months and MESAM after 34 (11 – 74) months				
Desaturation Index	13 (7 –98)	14 (0 – 75)	12 (1 – 87)	29
Response ≥ -50% DI		41%	31%**	29

Baseline data and follow-up data expressed as median and 95%-interpercentile range (95%-range). The last column shows the number of patients with complete data to allow analysis for the specific parameter. Desaturation parameters were analyzed in two groups: a group of patients with complete data on baseline and long-term follow-up only (n=38) and a group of patients with complete data on baseline, 6 months and long-term follow-up (n=29).
* = Compared with baseline p = 0.0001. Note ** = The difference in percentage of responders between 6 months and long-term is significant, p = 0.02. (The 6 months follow-up data were not subject of this study, but are included to allow comparison with long-term results.)

Snoring and excessive daytime sleepiness (EDS) were evaluated using a specially designed questionnaire with semi-quantitative scales (snoring coded 0 – 4 and daytime sleepiness coded 0 – 5, see Table 3.2 for details) (8,18). Desaturation parameters at baseline and at 6 months postsurgery were obtained by standard polysomnography, while long-term desaturation parameters were obtained by MESAM 4 (Madaus, Germany). The procedures are described in detail below. In 38 patients desaturation parameters were obtained at baseline and long-term follow-up. In 29 patients desaturation parameters were available on base line, 6 months and long-term follow-up. These two groups were analyzed separately. Response was defined as a reduction of at least 50% in oxygen desaturation index (ODI). A clinically relevant response was defined as a reduction of ODI from above to below 20 after treatment (19). Patients were considered cured if ODI was under 5 after treatment (20). Thirteen patients refused participation in long-term polygraphic follow-up and 7 recordings were of poor quality. In 17 patients no

recording was available at 6 months. Body Mass Index (BMI = kg/m^2) was calculated. Upper airway collapsibility and anatomy were assessed by the Mueller maneuver and X-cephalometry, following the procedures described in our earlier report (8). The Mueller maneuver was performed in the supine position, and the collapsibility at the level soft palate, the tongue base, and the difference in collapsibility between soft palate and tongue base were assessed and included in the analysis of pre-operative selection criteria. The X-cephalometric parameters included in this analysis were: the minimal posterior airway space at the level of the tongue base, the distance between the mandibular plane and the most cranio-ventral aspect of the hyoid bone, the length of the soft palate, being the distance of the posterior nasal spine to the tip of the uvula and the diameter of the soft palate taken at the widest point. All measurements were expressed in millimeters.

The baseline polygraphic recording included electroencephalography, electro-oculography and electromyography and sleep stages were scored following the international criteria of Rechtschaffen and Kales (21). Respiration was monitored by thermistors to assess oro-nasal flow, by impedance plethysmography to assess respiratory chest and abdominal excursions, and by pulse-oximetry to detect oxygen desaturation. Obstructive sleep apnea syndrome was defined as the presence of obstructive apneas during at least 10 seconds or more leading to 5 desaturations or more per hour of sleep. Periods with oxygen desaturation exceeding 3% reduction baseline were included in the calculation of the desaturation index (total desaturations/total sleep time per hour). The oxygen desaturation index (ODI) was used in our analysis.

The Madaus Electronic Sleep Analysing Machine type 4 (MESAM 4, Madaus, Germany) is a four-channel digital recording device (22,23). Oxygen saturation is measured using a pulse oximeter in a finger probe. Heart rate is monitored through a single lead ECG, by calculation of R-R intervals in milliseconds. Snoring sounds are monitored through a very small microphone (Conrad Electronics, Hirschau, Germany), which is taped above the larynx. Body position is monitored through a sensor applied on the lower part of the sternum. MESAM 4 provides information on heart rate variability, snoring spectrum, body position and nocturnal desaturation. An oxygen desaturation was defined as a desaturation of at least 4% from baseline during at least 10 seconds. If saturation has increased again to 95% of baseline level, the desaturation is considered ended. Every recording was scored by one of the investigators (HB). The patient noted the time of "lights-out" and "lights-on" on a accompanying sheet during the night of the recording. The total time considered for analysis was made more precise by taking the time between stabilization of heart rhythm after "lights-out" and the recurrence of irregular heart rhythm before "lights-on". Any period noted as awake by the patient or showing irregular heart rhythm and movement artifacts exceeding 30 minutes was left out of the final calculation of desaturation parameters. All automatically scored desaturations were individually inspected and artifacts were

removed from analysis. Only recordings with a minimal recording of five hours of good quality were included in the analysis. Recordings were performed at home and all patients received detailed information, and application of the different sensors was practised several times in hospital prior to the recording night.
For UPPP subjects were positioned as for tonsillectomy. The surgical procedure was performed under general anesthesia with a naso-tracheal intubation. The uvula was pulled towards the surgeon. The resulting natural horizontal crease in the pillar mucosa was used as the line for incision. The oral mucosa and sub-mucosa were removed, expanding laterally if a preoperative lateral collapse was found. The naso-pharyngeal mucosa and sub-mucosa were removed in the same manner, while the uvula itself was shortened, but not removed. If present, redundant tonsillar fossa mucosa and tonsillar tissue were also removed. The length of the uvula was trimmed if necessary, but not excised. The palatoglossal and palatopharyngeal muscles were spared during the procedure. Finally the posterior pillar was advanced and sutured to the anterior pillar with the suture line away from the nasopharynx. Nineteen patients underwent UPPP alone and 39 patients underwent UPPP in combination with tonsillectomy (UPPP + TE).
Baseline characteristics and follow-up data were not normally distributed, and are presented as median and 95%-interpercentile range. Improvement in snoring, daytime sleepiness, ODI and BMI was analysed with the Wilcoxon matched-pairs signed-ranks test. Differences in baseline data between groups in the ODI analysis were analyzed by the Mann-Whitney U test for unpaired data.
The relationship between post-operative changes and changes in BMI was analysed by regression analysis. The predictive value of any of the pre-operative parameters obtained by the Mueller maneuver, X-cephalometry and polysomnography was analysed by regression analysis, and its contribution to the variation in improvement of snoring, daytime sleepiness and desaturation index was estimated by calculation of r-square. The difference in improvement of snoring, daytime sleepiness, and ODI between UPPP and UPPP+TE treated patients was analyzed by the Mann-Whitney U test for unpaired data. P-values below 0.05 were considered to indicate significance.

4.4 Results

The absolute values of baseline and long-term follow-up data are listed in Table 4.1. Snoring improved at least one point in 63% of patients, no change was found in 23%, and 14% reported a deterioration of at least one point. The median improvement of snoring was one point (range: –4 to +2 points) and was highly significant ($p < 0.0001$). Daytime sleepiness improved at least one point in 38% of our patients, no change was found in 27%, while 35% showed a deterioration of at least one point. The median improvement of daytime sleepiness was 0 points (range:-5 to +3 points, $p = 0.80$).

Detailed information on ODI at baseline and long-term follow-up was available in 38 patients (see Table 4.1). ODI improved at least 50% in 13 of these patients (34%), a deterioration of 50% or more was found in 8 patients (21%) and no change in ODI (± 50%) was found in 17 patients (45%). The median change in ODI was –1 (95%-interpercentile range –73 to 51) and was not significant ($p = 0.35$). In 5 of the 13 patients showing improvement, ODI was reduced from above to below 20. Only 4 patients showed a reduction of ODI below 5 (ODI at baseline 7, 12, 13 and 35, respectively).

Age, snoring, daytime sleepiness and ODI at baseline and long-term follow-up were not different between patients with and without long-term polygraphic follow-up (all p-values > 0.10), but BMI in these patients was significantly lower at baseline (27.5 versus 31.0, $p = 0.02$) and at long-term follow-up (28.1 versus 32.0, $p = 0.049$). The change in BMI was not different between these patients.

In 29 patients information on ODI was available at baseline, 6 months and long-term follow-up. In this group the response rates at 6 months and long-term could be compared (see Table 2). The improvement of ODI between 6 months and long-term was significantly decreased during follow-up ($p = 0.02$). In the initial report 43 patients with ODI at baseline and 6 months were presented, 14 of these were not available for long-term polygraphic follow-up. Of the remaining 29 patients, 12 (41%) showed a reduction of at least 50% in ODI at 6 months and 9 (31%) patients showed this reduction at long-term. Seven patients showed this response after both 6 months and long-term. At 6 months, in only 5 patients the ODI was decreased below 20. Four of these patients remained responders according to this criterion. In 7 patients the ODI was < 5 at six months, 3 of these patients showed the same long-term response. One long-term responder with ODI < 5 was not a responder at 6 months.

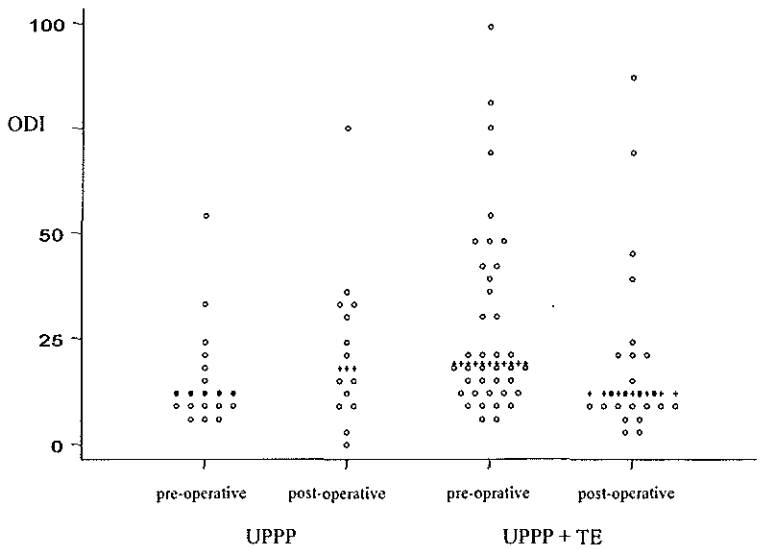
Body Mass Index (BMI) in our population did not change during follow-up (see Table 1) ($p = 0.54$). No relation between BMI and improvement of snoring ($p = 0.39$), daytime sleepiness ($p = 0.72$), or ODI ($p = 0.12$) was found. In only one responder a decrease in ODI from 29 to 19 to 12, a clinically relevant decrease in BMI was present (37.8 –31.0 – 31.6, at baseline, 6 months, and long-term respectively).

The upper airway collapsibility assessed by the Mueller maneuver at the level of the soft palate, the base of the tongue or the difference in collapsibility between soft palate and the base of the tongue were not related to treatment outcome. A relative long soft palate, as assessed by cephalometry, was related to improvement of daytime sleepiness and ODI, but its contribution was small (r-square = 0.09 and 0.13, respectively, and $p = 0.04$). A high preoperative ODI was related to a greater reduction of ODI (r-square = 0.34 and $p < 0.0001$), but not to improvement of snoring or daytime sleepiness.

Compared with UPPP alone, the improvement of snoring was better after UPPP combined with tonsillectomy (UPPP + TE), but the difference was not significant

(p = 0.06). The improvement of daytime sleepiness was not different between these two groups. UPPP + TE resulted in a significant decrease of ODI (median –7.5, 95%-interpercentile range –73 to +26, p = 0.02), compared to a non-significant increase after UPPP alone (median 4.5, 95%-interpercentile range –18 to +51, p = 0.10). The difference in improvement of ODI between UPPP + TE and UPPP alone was significant (p = 0.008, see Figure 4.1).

Figure 4.1.



Improvement of ODI after UPPP alone and after UPPP + TE. The horizontal lines with plus (+) signs mark the group medians. The increase in ODI in the UPPP group was not significant (p = 0.10). The decrease in ODI in the UPPP + TE group was significant (p = 0.02). The difference in change of ODI between the two groups was significant (p = 0.008).

4.5 Discussion

Our results show that snoring remains improved until years after UPPP for OSAS, but that daytime sleepiness relapsed. Although ODI did not improve significantly in our population, a minority of patients should be considered responders up to approximately 3 years after surgery.

Clinical symptoms are very relevant in the subjective rating of treatment outcome, but in the literature the response is usually defined by poly(somno)graphic criteria. Polysomnography is considered the standard for the diagnosis of OSAS, but other recording techniques have been used to evaluate the results of UPPP (24). We selected the ODI to evaluate postoperative response, because pulse-oximetry was

incorporated in our pre-operative polysomnographic (PSG) procedure and postoperative MESAM 4 registration. Oximetry has been shown to be useful in the detection of apneic events and the ODI obtained by automatic analysis with the MESAM 4 device reaches a specificity and sensitivity of 97% and 92%, respectively, for the identification of OSAS compared to the Respiratory Disturbance Index (apneas and hypopneas per hour sleep = RDI) $\geq$ 10 obtained by PSG (23,25). Manual scoring of the MESAM 4 recording was found to be even more accurate with a sensitivity of ODI of 97% to 100% (26,27). For these reasons we scored the MESAM 4 recordings by hand. These figures indicate that a 50% reduction of ODI equals a 50% reduction of apnea-hypopnea-index (AHI) or respiratory-distress-index (RDI), and this allows comparison with the literature.
The use of different recording techniques, different criteria for response, different follow-up periods and differences in patient selection complicate the interpretation of the results in studies on long-term follow-up after UPPP. All our patients had mild to severe OSAS and our population is therefore comparable to those in other papers. All but 5 patients had predominant collapse at the velo-pharyngeal level by the Mueller maneuver (8). This was an important selection criterion before considering UPPP as an option for treatment of OSAS in our patients The other studies on long-term results after UPPP seem to have included unselected patients, although this was specifically mentioned in one report only (11). The different criteria we used for response are based on the UPPP literature and on epidemiologic data on OSAS related morbidity and mortality. Reduction of at least 50% in ODI (Apnea-Hypopnea Index, RDI etc.) is generally used to define response, but other definitions may prove to be more useful (2). A reduction of ODI below 20 is based on the paper by He et al. who found increased mortality in untreated and UPPP treated patients with apnea index (AI) $\geq$ 20 (19). A reduction of ODI < 5 is based on our definition of OSAS as the presence of ODI $\geq$ 5 and on the findings of Hung et al. who showed an increased cardiovascular mortality if AI $\geq$ 5.3 (20).
Only a few papers on the long-term results of UPPP have been published. Larsson et al. evaluated 50 unselected consecutive patients at 6, 21 and 46 months after UPPP for OSAS (10,11). Response was defined as the combination of at least 50% reduction in ODI ($\geq$4%/hour), postoperative ODI < 20 and only minor drops in SaO_2 below 90%. He showed that the initial response rate at 6 months of 60% (30/50 patients) decreased to 40% (19/50 patients) after 21 months, and increased again to 50% (24/48 patients) after 46 months. Subjective improvement of EDS was reported in approximately 90% of patients and remained unchanged, but change in EDS was graded only as "complete recovery", "improvement" or "no improvement". A semi-quantitative estimate of actual improvement could therefore not be made. When we convert our results to the definition of response used by Larsson et al., 11/29 patients (40%) should be considered responders at 6 months and 10/38 (26%) at long term. Due to different presentation of baseline characteristics (mean versus median) we were not able to compare the two

populations, so the difference between improvement of ODI in the paper of Larsson et al. and our study remains largely unexplained. Since the reported complications are minor and comparable to our 6 months complications, the surgical approach by Larsson does not seem to have been more aggressive. In the study by Lu et al. response was defined as at least 50% reduction in respiratory disturbance index (RDI) (12). In the latter study 10/15 patients were considered responders after 3-12 months, while only 5/10 patients could be considered responders after 66-109 months. RDI increased significantly between initial and late follow-up ($p<0.05$). These long-term results are in concordance with our data. Subjective improvement was reported in 80% of patients, but snoring and EDS were again rated as "improvement", "no improvement" or "getting worse", not allowing quantifiable comparison with our results. None of their patients subjectively worsened with respect to snoring or EDS, which is in contrast to our data. Janson et al. studied 25 patients 6 months and 4-8 years after UPPP (13). Response was defined as 50% reduction in Apnea Hypopnea Index (AHI) and postoperative AHI below 10. After 6 months 16/25 patients (64%) were classified as responders versus 12/25 patients (48%) after 4-8 years. Despite the more narrow definition of response, the response rate is higher than in our study. The authors stated, however, that the high number of non-participants in the long-term follow-up had more severe OSAS and that inclusion of these patients might have lowered the response rate. Although no direct comparison can be made, their baseline data do not differ significantly from ours. Snoring and EDS were significantly reduced in the latter study, but again a different rating scale was used. No validated questionnaires for the evaluation of sleep apnea related snoring or daytime sleepiness were available, at the beginning of the present study. We used a different and specially designed semi-quantitative scale to assess severity of snoring and EDS both before and after treatment (18). Our results show for the first time an evident relapse of EDS to pre-operative levels after long-term follow-up. This finding corresponds well to the decrease in response as defined by different respiratory parameters. We did not find the inconsistency between the pronounced improvement of snoring and EDS versus the relatively small improvement of respiratory parameters that has been reported in most studies (8,28,29). A good explanation for this inconsistency is lacking, but it is possible that patients tend to attribute positive effects to a rather invasive treatment modality such as UPPP (30). This mechanism of attribution may also partly explain why subjective rating scales for snoring and EDS tend to overestimate improvement, when specifically asking for improvement, and this may explain why other studies reported more subjective improvement of snoring and EDS than we do (10-12). MESAM-4 provides an objective measure for snoring, discriminating "snoring" from "loud snoring" with a threshhold of 1.1 mV at 1000 Hz. Although this signal was found to be reliable in a soundproof chamber by Penzel et al. in 1990 (22), we found that it was very susceptible to other sounds generated by the bed partner and by friction of the blankets. This was the main

reason we decided not to use this parameter in our analysis. Furthermore, we believe that the discomfort experienced by the patient and his (her) bed partner is the most relevant aspect of snoring and this subjective improvement was a primary objective of this study.

We compared the response rates at 6 months and long-term follow-up by using the different definitions described earlier. Four of 5 patients with a decrease in ODI from above 20 to below 20 could be considered responders after 34 months, while only 3 of 7 patients maintained a response of ODI < 5. This means that the initially already insignificant cure rate in our patients decreases even more over the years. However, a small number of patients (7/38 = 18%) must still be considered good responders, even after 3 years of follow-up.

Only 38 of 58 patients participated in the long-term polygraphic recording and although these patients had significantly lower pre-operative BMI than the 20 non-participating patients, none of the postoperative changes could be related to pre-operative BMI or to post-operative changes in BMI. The results of this study are therefore not influenced by differences or changes in BMI. Only one study on long-term follow-up found a relation between a high pre-operative BMI and a low response to UPPP (10). Although this relation was not found by others (12,13), it can not be ruled out completely and this could mean that hypothetical inclusion of those patients without a full polygraphic follow-up in the analysis of ODI might have resulted in lower response rates in our study.

No clinically useful pre-operative selection criteria to identify good responders to UPPP have been found by analyzing the data obtained by the Mueller maneuver and cephalometry. The improvement of ODI was most pronounced in patients with a relative high pre-operative ODI, which is in concordance with our earlier report (8).

The improvement of ODI in UPPP + TE patients was significantly better compared to UPPP only patients. Eleven of the 13 patients showing more than 50% improvement of ODI underwent UPPP + TE. All 5 patients with a reduction in ODI from >20 to < 20, and 2 of the 4 patients with reduction of ODI below 5, did so after UPPP + TE. From an anatomical viewpoint, the presence of tonsillar tissue reduces the upper airway aperture and makes it more likely to collapse during inspiration. Although this mechanism is not supported by the finding of the Mueller maneuver, it is reflected by the higher sleep apnea severity as expressed in ODI between UPPP + TE and UPPP only patients at baseline (see Figure 1). Removal of this causative contributing factor may itself result in better improvement of ODI, but the resection of tissue in the tonsillar fossa results in a more lateral expansion of the incisure and consequently the suture line. A more generous resection of the soft palate may therefore be complementary to the effect of tonsillectomy alone and may contribute to better treatment outcome (31). Although it was not an objective of this study to evaluate this aspect, it is an important finding that may indicate that the presence of tonsillar tissue may be the only useful selection criterion for UPPP. However, not all UPPP + TE patients

were good responders, which indicates that other factors must contribute to treatment outcome.

We found that the initial results of UPPP for OSAS decrease progressively over the years. Snoring remained improved, although long-term results were slightly worse compared to 6 months results. Daytime sleepiness relapsed to pre-operative levels. Improvement of Oxygen Desaturation Index and response rates defined by different criteria deteriorated during long-term follow-up. UPPP remains effective in approximately 20% of patients only. Improvement of ODI was better after UPPP combined with tonsillectomy than after UPPP alone. Further research is needed to identify useful pre-operative criteria for selecting patients for UPPP. If such criteria could be established to identify these long-term responders before considering any kind of treatment, a considerable number of patients could profit from a single and relatively simple surgical procedure, while they would be spared years of troublesome treatment by CPAP.

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CHAPTER 5

Uvulopalatopharyngoplasty and Continuous Positive Airway Pressure for Obstructive Sleep Apnea Syndrome; a Prospective Randomised Trial

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5.1 Summary

Study Objectives: Comparing two strategies for the treatment of Obstructive Sleep Apnea Syndrome (OSAS); starting with Continuous Positive Airway pressure (CPAP) or starting with Uvulo-Palato-Pharyngo-Plasty (UPPP), with the possibility to switch to the other treatment modality, to evaluate which strategy results in better improvement of daytime sleepiness, quality of life, and nocturnal desaturations. *Design*: A randomised prospective trial using the Intention To Treat principle. *Setting*: Eight centers with a multi-disciplinairy approach of OSAS in the Netherlands. *Patients*: Subjects with complaints of daytime sleepiness caused by obstructive sleep apneas and predominant collaps of the upper airway at the level of the soft palate were included. *Interventions*: Patients were randomly allocated to UPPP or CPAP. *Measurements and Results*: Daytime sleepiness was scored using the Rotterdam Daytime Sleepiness Scale. Quality of life was assessed with the Nottingham Health Profile, the Hopkins Symptom Checklist, the Bradburn Affect Balance Scale and the Profile of Mood Scale. Desaturation parameters were obtained by MESAM-4. Immediate and consequential costs were distinguished. 125 Patients were included between November 1992 and May 1995. Follow-up ranged from 6 to 24 months. At the end of follow-up 77% of UPPP-first patients were switched to CPAP and 23% CPAP-first patients were switched to UPPP. We found no statistical significant differences in improvement of daytime sleepiness or quality of life. CPAP-first strategy resulted in early and better improvement of nocturnal desaturation. The mean direct costs per patient in the UPPP-first strategy is estimated at 5.257 US Dollars versus $ 2.802 per patient in the CPAP first strategy ($p \leq 0.02$). The cumulative consequential costs per patient in the UPPP-first strategy is estimated at $ 6.019 versus $ 2.052 in the CPAP-first strategy ($p \leq 0.08$). *Conclusions*: This study shows that treatment of OSAS in patients with predominant collaps at the velopharyngeal level should start with CPAP.

5.2 Introduction

A treatment strategy for Obstructive Sleep Apnea Syndrome (OSAS), comparing Continuous Positive Airway Pressure (CPAP) with Uvulopalatopharyngoplasty (UPPP) as the initial treatment modality has never been evaluated in a single randomised prospective study. UPPP and CPAP were both introduced in 1981 for the treatment of OSAS (1,2), but most studies conducted since report non-randomised single treatment results. CPAP is considered the treatment of first choice, but a selective group of patients with predominant collaps of the velopharyngeal airway can be treated by UPPP effectively (3). It is still unclear whether treatment of these patients should be

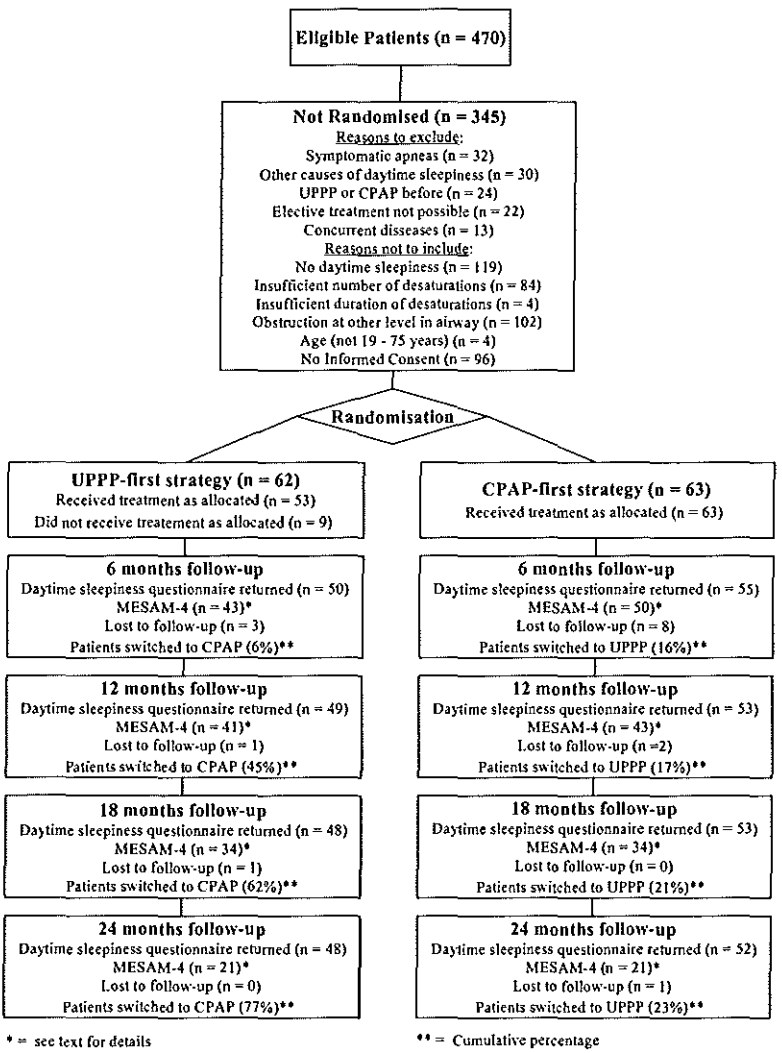
started with UPPP or CPAP, with the opportunity to switch to the other therapy in case of treatment failure.
To answer this question we evaluated two treatment strategies in a randomised prospective trial. In the UPPP-first strategy treatment was started with UPPP, with the possibility to switch to CPAP if insufficient improvement of OSAS was reached. In the CPAP-first strategy the initial treatment was CPAP with the possibility to switch to UPPP. The main questions to be answered were: how effective are both strategies in reducing excessive daytime sleepiness and improving quality of life? Secondary questions to be answered were: how effective are both strategies in reducing nocturnal oxygen desaturations; in which strategy will the number of therapy switches be smaller; which of both strategies has the best results in a cost-minimalisation analysis?

5.3 Materials and Methods

Patients with complaints of daytime sleepiness caused by obstructive sleep apneas and predominant collaps of the upper airway at the level of the soft-palate were eligible for the study. Diagnosis of OSAS had to be confirmed by standard polysomnography. OSAS was defined as the presence of at least 5 oxygen desaturations exceeding 4% from base line per hour (ODI), caused by obstructive apneas of at least 10 seconds. Frequency of reasons for not including or for excluding patients are listed in figure 5.1.
Two treatment strategies were evaluated, UPPP-first versus CPAP-first. Treatment failure was defined as: insufficient improvement of daytime sleepiness as judged by the patient; insufficient improvement of nocturnal desaturations as judged by the investigator and as intolerance to further treatment with CPAP. Switching from UPPP to CPAP (UPPP-first strategy) was allowed after 6 months only, to be sure that incomplete healing of the operation wound was not responsible for persistent daytime complaints. Switching from CPAP to UPPP (CPAP-first strategy) was allowed anytime during the follow-up. The protocol was approved by the ethics committees of all participating institutions.
The sample size of 2 x 37 = 74 patients was calculated on the basis of the following assumptions: the succes rate of UPPP defined as at least 50% reduction in ODI was estimated to be 50% (=p1); the succes rate of CPAP was estimated to be 80% reduction in ODI (=p2); $\alpha = 0.05$ (two-sided) and $\beta = 0.20$ (4). In order to obtain smaller confidence intervals of calculated differences between the two strategies, allowing more accurate interpretation of results for decision making in public health care, we aimed at including 150 patients. However a maximal study period of 3 years existing of a 2.5 years intake period and a minimal follow-up of 0.5 year was a preset limit, potentially restricting the number of included patients. The duration of the study was defined by

regulations of the health care technology assessment program of the Investigative Medicine Committee of the Dutch Health Insurance Council.

Figure 5.1.



Flow-chart describing the progress of patients through this trial, from eligible patients to number of patients available for statistical analysis during the follow-up visits. The reasons for exclusion or non-inclusion are listed in the second box from the top.

Randomisation was centralised. The investigators telephoned the coordinating centre and the patients were then assigned treatment strategies, according to a "block-wise" randomisation procedure for each participating institution. Eight centers with an experienced multi-disciplinairy approach of OSAS participated. The inclusion started on the first of november 1992 and ended on the first of may 1995. The formal follow-up closed 6 months later on the first of november 1995. In addition all patients were contacted by telephone to complete data on daytime sleepiness and actual therapy in december 1997, 2.5 years after inclusion of the last patient.

Data were obtained on moment of randomisation (base-line), and 6, 12, 18 and 24 months after start of therapy. The date of operation was start of therapy in the UPPP-first strategy. The first day following a successful habituation period was start of therapy in the CPAP-first strategy. Daytime sleepiness was scored using a four points subscale of the Rotterdam Daytime Sleepiness Scale (0 = no daytime sleepiness, 1 = once per week, 2 = several times per week and 4 = every day) (5). Quality of life was assessed with the Dutch translated and evaluated versions of the Nottingham Health Profile (NHP), the somatic subscale of the Hopkins Symptom Checklist (SOMAT), the Bradburn Affect Balance Scale (ABS) and the Profile of Mood Scale (POMS). Desaturation parameters were obtained by ambulatory registration using the MESAM-4 device. A standard physical examination was performed on every visit. Mueller manoeuvre and Roentgenographic cephalometry were performed before randomisation only. The Mueller manoeuvre was used to select patients with predominant collaps at the level of the soft palate (6). The treatment related costs of both strategies were distinguished in immediate and consequential. The immediate costs are composed of: days of hospitalisation, any medical treatment consumed (UPPP, CPAP and OSAS related), outpatient contacts (visits and telephone) and days on CPAP. The consequential costs were calculated from data obtained by a questionnaire designed by the Institute for Medical Technology Assessment (iMTA) and are composed of loss per day of non productivity as assessed by age related contribution to the bruto national income measure. The difference in total costs between the two strategies was assessed.

We used the Madaus Electronic Sleep Analysing Machine type 4 (MESAM 4) (Madaus, Germany), a four channel digital recording device (7,8). Oxygen saturation is measured using a pulse oximeter in a finger probe. Heart rate is monitored through a single lead ECG, by calculation of R-R intervals in milliseconds. Snoring Sounds are monitored through a very small microphone from Conrad Electronics, Hirschau, Germany. This microphone is taped above the larynx. Body position is monitored through a sensor applied on the lower part of the sternum. MESAM 4 provides detailed information on heart rate variability, snoring spectrum, body position and nocturnal desaturation. The ODI expresses the number of oxygen desaturations ≥ 4 percent from base line saturation per hour of analysed time. An oxygen desaturation was defined as a desaturation of at least

4% from base line during at least 10 seconds. As saturation has progressed to 95% of base line level, the desaturation is considered ended. Every recording was scored by one of the investigators (HB), who was unaware of the treatment strategy. We calculated the ODI, baseline desaturation,mean saturation, lowest saturation and the percentage of evaluation time with saturation below 90%. The patient noted the time of "lights-out" and "lights-on" on a accompanying sheet during the night of the registration. The total time considered for analysis was further precised by taking the point of stabilisation of heart rhythm after "lights-out" as start and the recurrence of irregular heart rhythm before "lights-on" as end of the evaluation period. Any period noted as awake by the patient or showing irregular heart rhythm and movement artifacts exceeding 30 minutes was left out of the final calculation of desaturation parameters. All desaturations were individually inspected and artifacts were removed from analysis. A minimal of five hours of registration of good quality was requiered. Since the MESAM 4 is an ambulatory device, all registration were performed at home. All patients received detailed information and application of the different sensors was practised several times in hospital prior to the registration night.

For UPPP subjects were positioned as for tonsillectomy. The surgical procedure was performed under general anesthesia with a naso-tracheal intubation. The uvula was pulled towards the surgeon. The resulting natural horizontal crease in the pillar mucosa was used as the line for incision. The oral side of the palatal mucosa and sub-mucosa were removed, expanding laterally if a pre-operative lateral collapse was found. The naso-pharyngeal side of the palatal mucosa and sub-mucosa were not removed. The uvula itself was shortened, if necessary, but not removed. If present, redundant tonsillar fossa mucosa and tonsillar tissue were also removed. The palatoglossal and palatopharyngeal muscles were spared during the procedure. Finally the posterior pillar was advanced and sutured to the anterior pillar with the suture line away from the nasopharynx. A UPPP-committee set up the protocol and monitored all procedures to reduce variability between the institutions.

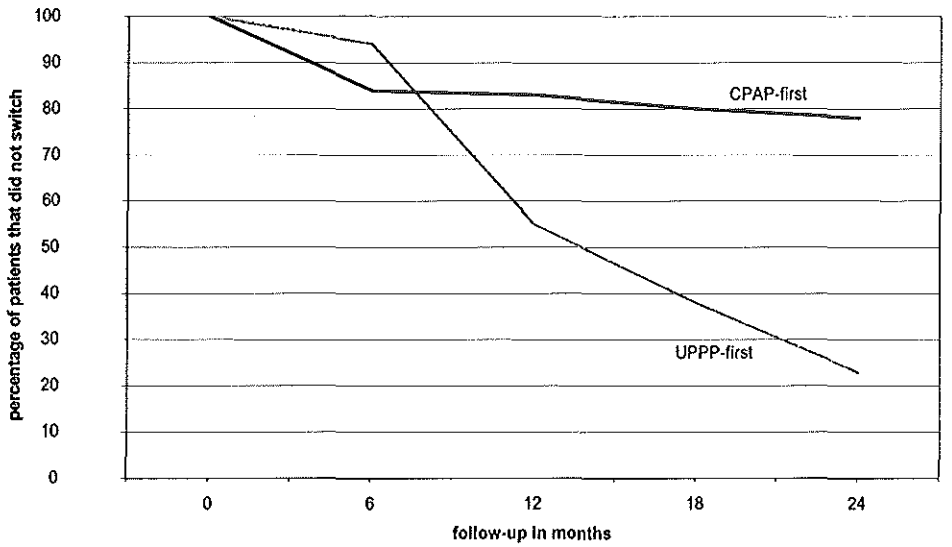
The REMSTAR-plus® from Respironics was used in all patients on CPAP. A BIPAP®-device (Respironics Inc; Murrysville, Pa) could be used if necessary. Humidifiers were prescribed without restrictions and all types of masks were allowed. Three different procedures were used to determine the optimal inspiratory pressure: clinical titration during one night, clinical titration during several nights and titration at home with support in an outpatient setting. The habituation period consisted of support by telephone and repetitive visits in a outpatient setting. The institutions were allowed to follow their own procedures according to their experiences and to the wishes of their patients. Titration and habituation were succesful if the patient was satisfied with the improvement of daytime sleepiness and no further improvement in nocturnal desaturation could be obtained by increasing pressure. A CPAP-committee monitored all procedures and advised in case of habituation problems.

We defined as primary end-point: improvement of at least one point on the 4-point daytime sleepiness scale. Secondary end-points are: treatment failure (switche of therapy); improvement of at least one point on any subscale of the quality of life questionnaires; the absolute improvement of desaturation parameters (especially the ODI); 50% reduction in ODI and ODI below 20 (criterion A "improved") (9); 50% reduction in ODI and ODI below 5 (criterion B "cured") (10,11). Continuous outcomes were compared within groups with the matched-pairs signed-rank test of Wilcoxon, and between groups with the Mann-Whitney U test. Percentages between groups were compared with the chi-square test without correction for continuity. All analyses were performed using the Intention-To-Treat principle. An interim analysis was performed after 6 months of follow-up of the first 75 patients.

5.4 Results

The interim analysis showed no difference in improvement of daytime sleepiness on the 4-point sleepiness scale between the two strategies. In fact the results were similar as found in the larger sample as described below. The intake period was therefore closed after 2.5 years (as predetermined).
120 Men and 5 women (mean age 49 years, 95 interpercentile range 28 - 60) were included, 62 in the UPPP-first strategy and 63 in the CPAP-first strategy. There were nine drop-outs. In the UPPP-first strategy 7/62 patients refused operation and in one patient operation could not be performed within the defined period. In the CPAP-first strategy one protocol violation occurred by including a patient without daytime sleepines. Eleven other patients were excluded because the data at base-line or at six months follow-up did not allow statistical analysis. 105 Patients were therefore available for analysis of the primary end-point. After closure of the study we were able to complete data on actual therapy and daytime sleepiness in 48 of the 62 UPPP-first patients and in 52 of the 63 CPAP-first patients. All switches of therapy occurred within 24 months after inclusion.
At the end of follow-up 37 of 48 UPPP-first patients (77%) have been switched to CPAP. The reasons for switching were insufficient improvement of daytime sleepiness in 34 and insufficient improvement of nocturnal desaturation in 3 cases. 12 of 52 CPAP-first patients (23%) have been switched to UPPP at the end of follow-up. All patients reported CPAP-problems (pressure related in 2, mask related in 5, nasal congestion in 2 and general complaints in a total of 9), and in 3 cases insufficient improvement of daytime sleepiness was reported also. Figure 5.2 displays the percentage of patients that remained without switching in each strategy during the course of follow-up.

Figure 5.2.



Curve showing the percentage of patients that did not switch from therapy during follow-up in the UPPP-first and CPAP –first strategies.

Table 5.1.

Strategie	6 months	12 months	18 months	24 months
UPPP-first	64	71	81	76
CPAP-first	65	65	80	69
p-value	0.88	0.55	0.91	0.58

The percentage of patients per strategy with a decrease of at least one point on the four points daytime sleepiness scale.

Table 5.1 summarises the percentage of patients with improvement of daytime sleepiness. No significant differences between the two strategies were found.
The quality of life measurements showed significant improvement within both strategies on almost every subscale of the questionnaires used. The NHP and SOMAT showed no differences between the strategies. The ABS showed a significant difference in increase in positive experiences in the CPAP-first versus the UPPP-first strategy ($p = 0.02$) at 24 months. The POMS showed a significant, but very small difference in decrease of depression score in the UPPP-first versus the CPAP-first strategy ($p = 0.05$). No other significant differences were found.
The base line and follow-up data of desaturation parameters are summarised in table 5.2. In both strategies the ODI decreases after treatment. In the UPPP-

first strategy the decrease was only significant after 12 months ($p < 0.0003$, with median decreases of 19, 24.5 and 37 desaturations per hour on 12, 18 and 24 months respectively). The decrease in the CPAP-first strategy was significant from 6 months on ($p < 0.0008$, with median decreases of 19, 26, 27 and 26.5 respectively). The difference between the strategies was found to be significant at six months only. Table 5.3 summarises the improvement of ODI as defined by criterion A and B. The initial significant difference between the strategies disappeared during follow-up.
At the end of follow-up the mean direct costs per patient in the UPPP-first strategy is estimated at 5.257 US Dollars versus $ 2.802 per patient in the CPAP first strategy ($p \leq 0.02$). The cumulative consequential costs per patient in the UPPP-first strategy is estimated at $ 6.019 versus $ 2.052 in the CPAP-first strategy ($p \leq 0.08$).

Table 5.2.

	Base line	6 months	12 months	18 months	24 months
UPPP-first	n = 48	n = 43	n = 41	n = 34	n = 21
Base line SaO2	96 (88-98)	96 (90-98)	96 (93-98)	96 (90-98)	97 (94-98)
Mean SaO2	88 (61-93)*	89 (73-94)	90 (62-94)	92 (84-93)	91 (88-94)
Lowest SaO2	74 (41-90)*	77 (42-94)	84 (43-93)	87 (70-93)	87 (74-94)
Percentage < 90%	20 (0-95)*	10 (0-85)	2 (0-61)	1 (0-89)	1 (0-23)
Desaturation-index	39 (7-83)	27 (0-89)(2)	10 (0-56)(1)	10 (0-54)(1)	4 (0-37)(1)
CPAP-first	n = 50	n = 50	n = 43	n = 34	n = 21
Base line SaO2	96 (91-98)	97 (90-98)	97 (94-98)	97 (93-98)	96 (91-98)
Mean SaO2	90 (74-94)*	92 (85-94)	92 (87-95)	92 (87-96)	92 (86-93)
Lowest SaO2	80 (42-91)*	87 (65-93)	88 (58-94)	88 (70-95)	88 (78-93)
Percentage < 90%	5 (0-84)*	0 (0-31)	0 (0-15)	0 (0-31)	0 (0-87)
Desaturation-index	26 (2-90)	3 (0-43)(1)(2)	3 (0-45)(1)	2 (0-32)(1)	5 (0-30)(1)

All desaturation parameters obtained by MESAM-4. The median and 95%-interpercentile range are shown. The differences at base line that were found to be significant between strategies are marked by (*). The desaturation-index is used in the comparative analysis only. The significant improvement within each strategy is marked by (1), $p < 0.0008$. The significant difference in improvement between strategies is marked by (2), $p = 0.0005$.

Table 5.3.

	6 months	12 months	18 months	24 months
Criterion A				
UPPP-first	12%	44%	65%	76%
CPAP-first	77%	79%	77%	65%
p	<0.0001	0.001	NS	NS
Criterion B				
UPPP-first	5%	13%	29%	57%
CPAP-first	55%	55%	67%	45%
p	<0.0001	<0.0001	0.002	NS

The percentage of patients showing 50% decrease in Oxygen Desaturation Index (ODI) and ODI below 20 (Criterion A) and 50% decrease in ODI and ODI below 5 (Criterion B).

5.5 Discussion

This is the first prospective randomised multi-centre trial comparing CPAP and UPPP as alternative treatments in patients with OSAS and predominant obstruction at the level of the soft palate. We found that CPAP is to be preferred over UPPP as the initial treatment of OSAS because, it is better accepted by patients, it leads to a better and faster improvement of nocturnal desaturations, and it is cheaper. Improvement of daytime sleepiness was equally large in both strategies. Measures of quality of life were marginally better in the CPAP-first strategy.

An important value of this study is, that it was designed to represent the situation in everyday clinical practice where both UPPP and CPAP are available for treatment of OSAS. The design of our protocol allowed therefore a change of therapy in case of insufficient improvement in daytime complaints and nocturnal saturation. Within the conditions of the protocol every patient was able to select the treatment with the optimal individual result. This proces of pragmatic self-selection resulted in an increasing similarity in all outcome parameters between the two strategies during follow-up. Due to this approach, the results of this study will be easily implemented in the routine treatment of patients with OSAS.

Several aspects of this study should be considered. From the beginning we were more interested in investigating the difference in improvement of daytime sleepiness and quality of life than in the difference in desaturation parameters between the two strategies. However no detailed data on improvement of daytime sleepiness and quality of life after either UPPP or CPAP were available in the literature to estimate the difference in improvement for calculation of sample size at that time. Sample size was calculated on an estimated difference in desaturation index. This means that the power of the study may not be enough to rule out that small differences in improvement in daytime sleepiness and quality of life exist between the two strategies.

As explained earlier, the fixed study duration had its influence on the number of inclusions as well. There were nine drop-outs, seven of whom refused operation after being assigned to UPPP. We consider it likely that these subjects consented to participation in the hope to be assigned to treatment with CPAP. During this study CPAP-treatment was not easily refunded in the Netherlands. The base-line characteristics of the drop-out were not different from the whole group.

Our data show that over 75% of patients in the UPPP-first strategy were switched to CPAP after 24 months, while less than 25% of patients in the CPAP-first strategy were switched to UPPP. This means that on the long run approximately 75% of all patients will be treated by CPAP, independent of the initial therapy. Eight of the 12 switches from CPAP to UPPP occurred in a single institution. This centre included 15 patients in the CPAP-first strategy.

No differences in improvement of daytime sleepiness or nocturnal desaturations between these particular patients and the others were present, so no bias was caused by this subgroup of patients. A substantial part of switches from CPAP to UPPP is however caused by a local policy. This indicates that over all less patients will switch from CPAP to UPPP, than our data suggest.
The improvement in daytime sleepiness was impressive in both treatment strategies. The process of self-selection can explain why no differences were found between the two strategies. Insufficient improvement of daytime sleepiness was the main reason for switching from UPPP to CPAP (34 of 37 cases), while only 3 of 12 patients switched from CPAP to UPPP for this reason. Considering that eventually 75% of both strategies existed of CPAP-treated patients, it was very unlikely that any difference would develop during follow-up, especially when we realise that all those patients who did not switch from therapy were sufficiently treated with respect to desaturation parameters (details on results per treatment are not given, but will be published separately).
In this context it is hard to explain why we did not find a difference in improvement of daytime sleepiness at 6 months, where the difference in improvement of ODI was much better in the CPAP-first strategy. Four possible explanations exist. From the literature we know that the improvement of daytime sleepiness after UPPP may be impressive on short-term follow-up, but that complaints tend to recurr after 6 – 18 months (12). It is also possible that following any surgical procedure, patients tend to over estimate the improvement of their complaints. This proces is hypothesised on the basis of the "cognitive dissonance" theory. This theory assumes that persons have a drive to mental consistancy. Two conditions (to undergo a surgical procedure and, at the other hand, the improvement perceived) need to be brought into harmony, otherwise mental discomfort arises (13). Discomfort of using CPAP during the night may influence sleep quality and as a consequence the improvement of daytime sleepiness will not be maximal. The same discomfort of CPAP will reduce patient compliance with additional decrease of efficacy (14-18).
All the scores on base line indicate a low quality of life, that improves drasticly and significantly in both strategies. Because the data on quality of life are so extensive, they are not presented here in detail. Some parameters showed a better improvement in the CPAP-strategy. These differences were however not consistent over all scales and domains. There is however a tendency towards better improvement in the CPAP-first strategy.
We used the MESAM-4 to obtain detailed information on nocturnal oxygen desaturation. Although the absence of sleep parameters, airflow and respiratory movements limits the use of the MESAM-4 as a diagnostic tool, it is valuable for research purposes. The comparison of desaturation parameters is relatively unbiased due to the automatic analysis. We selected the oxygen desaturation index (ODI), for our final analysis, because it is easily reproduced and comes as

close to the apnea index as possible (8). At base line the differences in mean SaO_2, lowest SaO_2 and percentage of registration time with SaO_2 below 90% between the two strategies were significant but small (see teble 4.). The difference in ODI at base-line was however not significant. At six months the difference in improvement of ODI is significantly in advantage of CPAP-first strategy. This is the only moment during follow-up where the relatively pure UPPP and CPAP results can be compaired, because no switches from UPPP to CPAP occurred yet. The improvement in the UPPP-first strategy was small and not significant, while the improvement in the CPAP-first strategy was impressive. This is in concordance with data from the literature (3,19). Later in the follow-up the initial difference disappears as a result of the self-selection proces.

It is not clear from the literature when we should consider patients sufficiently treated (20). Several criteria are proposed. Based on epidemiologic data concerning cardiovascular complications and death from OSAS, we defined two criteria. We defined a reduction of at least 50% in ODI and ODI after treatment below 20 as a good respons (Criterion A) (9), and a reduction of at least 50% and ODI after treatment below 5 as curative (Criterion B) (10). Our results show that the process of self-selection is so effective that after 24 months of follow-up no differences between the two strategies exist. It is however important to notice that the 6-months improvement in the CPAP-first strategy is 77% for criterion A and close to 55% for criterion B and that this remains rather unchanged during follow-up. In the UPPP-first strategy over two years of treatment were needed to reach similar results (table 5).

The cost-minimalisation anlysis shows that starting treatment with CPAP is cheaper than starting treatment with UPPP, although the difference in consequential costs is not significant. Two exceptional cases were however left out of the analysis. In the UPPP-strategy a traumatic intubation led to prolonged medical consumption ($ 9.175). This complication is UPPP related. In the CPAP-first strategy a serious cardio-vascular event resulted in several surgical interventions in one patient ($ 34.061). This complication is considered OSAS-related, but not direct CPAP related. If we include the costs of the UPPP-related complication, total costs per patient in the UPPP-first strategy will even be higher and the difference between the strategies will even be more impressive.

This study shows that treatment of OSAS in patients with predominant collaps at the velopharyngeal level should begin with CPAP. UPPP should be reserved for selected patients who do not tolerate CPAP.

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CHAPTER 6

Quality of Life in Patients with Obstructive Sleep Apnea Syndrome; A prospective Randomised Trial comparing Uvulo-Palato-Pharyngoplasty and Continuous Positive Airway Pressure

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6.1 Abstract

Recently the results of the first prospective randomised study comparing Uvulo-Palato-Pharyngoplasty (UPPP) and Continuous Positive Airway Pressure (CPAP) in the treatment of Obstructive Sleep Apnea Syndrome (OSAS) have been described. No difference in improvement of daytime sleepiness was found, but CPAP resulted in significantly better improvement of nocturnal desaturation, was better accepted by patients, and was superior in a cost-minimalisation anlysis. A prospective evaluation of the effect of UPPP and CPAP on Quality of Life (QoL) parameters has never been described.
The aims of this study were to evaluate QoL in untreated patients and to compare the effect of treatment with either UPPP or CPAP. We analysed 105 of 125 patients with polysomnographically documented OSAS and daytime sleepiness. In case of treatment failure, patients switched to the other treatment. We performed an analysis following the Intention-To-Treat principle (ITT), comparing UPPP-first with CPAP-first treated patients and an As Treated analysis (AT), comparing UPPP, CPAP,CPAP after UPPP, and UPPP after CPAP.. QoL was assessed at base-line and 6, 12, 18 and 24 months, with the Nottingham Health Profile part 1 (NHP part1), the Somatic subscale of the Hopkins Symptom Checklist (SOMAT), the Bradburn Affect Balance Scale (ABS), and the Profile of Mood States (POMS).
The base-line scores on all subscales of the NHP part 1, SOMAT, ABS, and POMS were found to be in the range of diseased to severely diseased norm groups. In the ITT analysis a statistically significant improvement was found on almost all subscales, but mean scores were still in the diseased range. The overall comparison of the UPPP first and CPAP first treated patients showed no statistically significant differences in improvement of QoL. CPAP first treated patients however, tended to show a better respons. In the AT analysis the differences between UPPP, CPAP, CPAP after UPPP, and UPPP after CPAP were not significant.
QoL is severely affected in patients with OSAS, and treatment with UPPP or CPAP results in a considerable improvement, but without restoring QoL to normal values.

6.2 Introduction

Although the symptoms and sequelaea of Obstructive Seep Apnea Syndrome (OSAS) may have devastating consequences for the lives of those affected (1), quality of life before and after treatment with either Uvulo-Palato-Pharyngoplasty (UPPP) or Continuous Positive Airway pressure (CPAP) has scarcely been investigated (2-4). Since the introduction of both UPPP and CPAP for the treatment of OSAS in 1981 (5,6), the effectiveness of treatment

has mainly been assessed by changes in snoring, daytime sleepiness, nocturnal desaturation and respiratory parameters (7). Recently we described the first prospective randomised clinical study (The Dutch Sleep Apnea Study) comparing two treatment strategies for OSAS, comparing UPPP and CPAP in 125 patients with mild to severe OSAS (Chapter 5). We found no differences in improvement of daytime sleepiness between the UPPP and CPAP strategies, but CPAP resulted in significantly better improvement of nocturnal desaturation. The inconsistency between improvement of subjective daytime complaints and objective respiratory parameters in UPPP-treated patients has been reported earlier (8-10). Furthermore the improvement of respiratory parameters was not found to be invariably related to improvement of sleep architecture and daytime function in CPAP-treated patients (11-13). We wanted to investigate whether the difference in improvement of respiratory parameters between UPPP and CPAP was also present in Quality of Life parameters or that the same inconsistency between subjective and objective improvement was present.
The aims of this study were therefore to evaluate Quality of Life (QoL) before and after treatment of OSAS and to assess the differences in changes in QoL between UPPP and CPAP treated patients. The QoL measures were compared to norm values, both before and after treatment to describe the impact of OSAS on QoL and the clinical relevance of changes in QoL. Because no evaluated disease specific questionnaires to assess QoL in OSAS existed at the time we started this study (2,3,14), we selected the Nottingham Health Profile part 1, the Somatic sub-scale of the Hopkins Symptom Checklist, the Bradburn Affect Balance Scale, and the Profile of Mood States, as generic and domain-specific measures for QoL and somatic and psychological well-being.

6.3 Materials and Methods

We performed a prospective randomised clinical multi-centre trial to assess the efficacy of UPPP and CPAP in the treatment of OSAS in the Netherlands. The study design is described in detail in our earlier report (Chapter 5).
We included patients with daytime sleepiness caused by obstructive sleep apnea syndrome defined as the presence of at least 5 oxygen desaturations exceeding 4% from base line per hour of sleep (ODI), caused by obstructive apneas of at least 10 seconds. All patients had predominant collaps of the upper airway at the velopharyngeal airway by Mueller manoeuvre. Two treatment strategies were evaluated: starting treatment with UPPP versus starting treatment with CPAP-first. In case of treatment failure, defined as: insufficient improvement of daytime sleepiness as judged by the patient; insufficient improvement of nocturnal desaturations as judged by the investigator and as intolerance to further treatment with CPAP, patients could switch to the other treatment modality (chapter 5). The inclusion started on the first of november 1992 and

ended on the first of may 1995.
Data were obtained on moment of randomisation (base-line), and 6, 12, 18 and 24 months after start of therapy. The procedures for UPPP and CPAP are described earlier (chapter 5).
QoL was assessed in a generic way with the Dutch translated and evaluated versions of the Nottingham Health Profile part 1 (NHP part 1) ,and in a domain specific way, focussing on somatic and psychological well-being with the Somatic subscale of the Hopkins Symptom Checklist (SOMAT), the Bradburn Affect Balance Scale (ABS) and the shortened Profile of Mood Scale (POMS) in reliable and validated Dutch versions.
The NHP part 1 is composed of several subscales: Emotional Respons (ER), Pain (P), Energy (E), Sleep (S), Social Isolation (SI) and Physical Mobility (PM), all referring to different health aspects. Every subscale is scored seperately following the criteria defined in the manual (15). A high score on every subscale indicates that this specific aspect of phsychological and physical well-being is more affected by any underlying illness. Erdman presented norm values for diseased and healthy subjects obtained from 276 patients from a general practitioners population in the Netherlands (15). He distinguished four groups: men < 50 years, men ≥ 50, women < 50 and women ≥ 50. Due to the male predominance and the median age of 49 of our population, we compare our data to recalculated mean scores for the entire male population from Erdman. These recalculated scores are displayed in table 6.2.
The SOMAT is composed of 8 questions referring to somatic complaints. Every item can be scored from 0 to 3 (not at all – very much). The total score is obtained by summation of the subscores (16). A high score indicates more physical complaints resulting in more dysfunctioning during daytime activities. The scores for the translated Dutch SOMAT were normated for 3 populations (normals, psychiatric patients, and psycho-somatic patients). The results are summarised in the manual by Luteijn in 1984 (16). We compare our results to the sore found in normals (see table 6.3).
The ABS is composed of 5 positive and 5 negative items, reflecting positive and negative experiences/feelings respectively. Each item can be denied or confirmed. The total score per item is obtained by summation of the confirmative answers. No norm scores were available for comparison with our data.
The POMS measures five dimensions: Depression (8 items), Anger (7 items), Fatigue (6 items), Vigor (5 items) and Tension (6 items). Every item can be scored 0 to 4 (17). A total score per dimension is calculated by summation of the item scores. A high score indicates that the specific dimension is more affected. Wald et al. presented scores obtained in 1984 from 481 men and 491 women in a general practitioners practice. We compared our data to the scores in the male population. These scores are displayed in table 6.3.
Due to the study design we performed our analysis using the Intention-To-Treat

principle and the As-Treated principle. Using the Intention-To-Treat principle two treatment strategies were compared: starting treatment of OSAS with UPPP (including all patients switching to CPAP during follow-up) versus starting treatment with CPAP (including all switchers to UPPP). These two strategies will be referred to as: UPPP-first strategy and CPAP-first strategie. Using the As-Treated principle four therapy groups are compared: UPPP, CPAP, CPAP after UPPP, and UPPP after CPAP. During follow-up the composition of every therapy group is changing, because between every follow-up visit patients switched from therapy.
The change in QoL is defined as the difference between the scores on every subscale during follow-up and the scores on base-line. In the "Intention-To-Treat-analysis" (ITT) the changes of QoL within the UPPP-first and the CPAP-first strategies were compared to base-line with the matched-pairs signed-rank test of Wilcoxon and the differences in changes between the two strategies were compared with the Mann-Whitney U test. In the "As-Treated analysis" (AT) the changes of QoL within each therapy group were compared with matched-pairs signed-rank test of Wilcoxon and the differences between the therapy groups by Kruskal-Wallis. The ITT analysis was considered most important, because it reflects every day clinical practice where patients seek the best treatment for their complaints in dialogue with their physician. The ITT analysis is therefore presented in detail, while the AT analysis is presented briefly to assess differences in the netto effect of UPPP and CPAP.

Table 6.1.

	Base-line	6 Months	12 Months	18 Months	24 Months
Intention-To-Treat analysis					
UPPP-first	62	50	43	35	25
CPAP-first	63	55	45	40	25
As-Treated analysis					
UPPP		47	26	15	8
CPAP		46	38	34	22
CPAP after UPPP		3	17	20	17
UPPP after CPAP		9	7	6	3

The number of patients in each strategy and treatment group that were available for analysis on base-line and every follow-up visit. The progressive decrease in patients is due to the limited study duration. In the As Treated analysis no base-line data are presented, because of the changing composition of each treatment-group as a result of switching from treatment modality during follow-up.

6.4 Results

Hundred and twenty men and 5 women were included with median age of 49 years (95%-interpercentile range 28- 70). All patients were sleepy according to the Rotterdam Daytime Sleepiness Scale (RDSS) (18). Median desaturation index was 32.5 (95%-interpercentile range 5 – 90). The anthropometric data were described in detail earlier (chapter 5). There were nine drop-outs and 11 patients were excluded because their questionnaires did not allow full statistical analysis. The remaining 105 questionnaires were suitable for analysis.
The number of patients decreases progressively during follow-up, due to the limited duration of the study. The numbers of patients available for analysis are displayed in table 6.1.

Table 6.2.

	Base-line	6 Months	p	12 Months	p	18 Months	P	24 Months	p
Emotional Response (diseased score 11.7, healthy score 3.2)									
UPPP	27.1(27.5)	16.2(25.0)	0.01	13.0(24.5)	0.005	15.2(27.6)	0.01	19.6(25.7)	<0.02
CPAP	31.3(25.6)	15.6(26.1)	<0.0001	14.8(24.4)	0.003	13.1(19.0)	0.0005	12.5(22.1)	0.008
p	NS	NS		NS		NS		NS	
Pain (diseased score 8.6, healthy score 4.4)									
UPPP	17.4(27.4)	16.4(25.0)	NS	14.7(25.6)	NS	22.5(33.2)	NS	20.0(29.1)	NS
CPAP	20.2(27.5)	16.6(30.4)	NS	12.7(24.1)	0.07	15.4(26.8)	NS	11.5(26.7)	NS
p	NS	NS		NS		NS		NS	
Energy (diseased score 12.7, healthy score 5.0)									
UPPP	55.4(37.5)	26.7(37.5)	0.0001	24.8(36.5)	0.002	24.8(37.3)	0.0001	29.3(37.7)	<0.005
CPAP	60.6(38.1)	24.2(38.2)	<0.0001	20.0(34.4)	<0.0001	20.8(34.3)	<0.0001	23.6(37.4)	0.0004
p	NS	NS		NS		NS		NS	
Sleep (diseased score 10.9, healthy score 9.2)									
UPPP	26.6(24.7)	16.9(23.4)	0.03	20.9(22.2)	0.07	18.9(22.2)	0.07	16.8(19.7)	<0.01
CPAP	25.3(25.1)	13.8(20.0)	0.0007	9.3(14.5)	0.0002	14.5(21.2)	<0.02	9.6(18.4)	0.01
p	NS	NS		NS		NS		NS	
Social Isolation (diseased score 6.2, healthy score 1.5)									
UPPP	14.9(23.4)	8.4(19.0)	NS	6.5(17.3)	0.02	9.7(22.9)	NS	11.2(20.9)	0.04
CPAP	14.1(17.4)	6.5(17.2)	<0.003	4.0(10.1)	0.001	2.5(9.3)	0.005	4.8(11.9)	0.006
p	NS	NS		NS		NS		NS	
Physical Mobility (diseased score 9.0, healthy score 3.7)									
UPPP	20.5(23.9)	16.8(21.7)	0.07	12.5(17.7)	0.01	17.1(25.4)	<0.10	17.5(19.8)	0.09
CPAP	15.1(20.8)	13.7(21.3)	NS	9.8(15.3)	NS	8.4(15.9)	0.03	7.5(16.9)	<0.01
p	NS	NS		NS		NS		NS	

The absolute scores with their standard deviation between brackets on every subscale of the NHP part 1 in the UPPP-first strategy (UPPP) and the CPAP-first strategy (CPAP). The level of significance (Wilcoxon signed-rank) of the improvement of every score is displayed in the column following every follow-up visit (vertically). The level of significance of the difference in improvement between the two strategies (Mann-Whitney U) is displayed in the last row of the corresponding score (horizontally). NS means not significant and no trend ($p > 0.10$). The norm scores for diseased and healthy persons are derived from Erdman 1994 (15) and are displayed between brackets behind the title of every subscale.

6.4.1 Intention-To-Treat Analysis

The scores on the NHP part 1 are shown in table 6.2. Compared to the norm scores by Erdman, our scores at base-line exceeded these values by almost 2 to 3 times. Almost all scores decreased significantly after treatment in both strategies. No statistically significant differences in improvement of any of the scores was found between the two strategies, but almost all scores were lower in the CPAP-first strategy on every follow-up. The Pain-score showed an increase, although not significant, in the UPPP-first strategy. Especially the improvement on the Energy-and Sleep-scores was salient.
The scores on the SOMAT are displayed in table 6.3. Base-line scores in both strategies were 2 to 3 times higher than the norm score by Luteijn et al, and were situated between the 80^{th} and 95^{th} percentile (16) The score decreased significantly in both strategies on almost every follow-up, but no statistically significant differences were found between the two strategies. UPPP-first scores were (insignificantly) lower during the first 12 months of follow-up and the CPAP-first scores in the second 12 months.
The scores on the ABS are displayed in table 6.3. A significant increase in positive experiences and a significant decrease in negative experiences was found in both strategies, but the improvement disappeared in the UPPP-first strategy. Only at 24 months a statistically significant difference in favor of CPAP was found between the strategies.
The results on the POMS are also displayed in table 6.3. Compared to the norm values by Wald et al.(17), all negative mood domains showed higher scores. Again all scores showed a significant improvement on almost every follow-up. Only one statistically significant difference and two trends in favor of CPAP first treated patients were found (depression at 6, anger at 12, and vigor at 24 months).

6.4.2 As-Treated Analysis

No statistically significant difference on any subscale was found at base-line. The number of patients in the CPAP after UPPP therapy group at 6 months and the UPPP after CPAP therapy group at 24 months were too small to allow statistical analysis (see table 6.1). None of the subscales of the four questionnaires used, showed statistically significant differences between any of the four therapy groups during the total follow-up time.
The NHP part 1 showed that an improvement was present in all groups, but most pronounced in the CPAP group. The differences between the groups were however small, and not significant. Patients in the CPAP after UPPP and UPPP after CPAP groups showed a smaller improvement than the other two groups. Patients in the UPPP group scored higher on Pain. The improvement of energy

was most pronounced in the CPAP and CPAP after UPPP groups.
The SOMAT showed a persistent and statistically significant decreased score in the CPAP group during the total follow-up. In the UPPP and UPPP after CPAP groups a statistically significant decrease was found during the first 12 months only. No change was found in the CPAP after UPPP group.
The increase in positive experiences and the decrease in negative experiences on the ABS were persistently significant during the total follow-up in the CPAP group only. In the other groups no trend was found in any direction.
The POMS showed a decrease in the domains of depression, anger, fatigue and tension in the UPPP and CPAP groups. Vigor increased in these two groups. In the CPAP after UPPP and UPPP after CPAP groups no persistent changes were found.

6.5 Discussion

Quality of Life in patients with OSAS is significantly improved after treatment with either UPPP or CPAP. The results of the NHP part 1, SOMAT, ABS and POMS all showed the same improvement and no differences were found between between UPPP and CPAP treated patients. The improvement of QoL was not influenced by switching from UPPP to CPAP or vice-versa.
We included patients with mild to severe OSAS. All patients complained of daytime sleepiness and were shown to have obstructive sleep apnea by polysomnography following the internationally accepted standards (19). Predominant collaps at the velo-pharyngeal level was the only selection criterion we used. Because the international "consensus", as reviewed by Sher in 1996, advised against UPPP in patients with predominant collaps of the upper airway at any other level (20), we considered it unethical to include these patients.
The study was designed to reflect every day clinical practice, allowing the dialogue between physician and patient to evaluate the effect of treatment and to switch from therapy if insufficient improvement of daytime sleepiness or nocturnal desaturation were present. At the end of follow-up over 75% of patients switched from UPPP to CPAP, compared to less than 25% from CPAP to UPPP (chapter 5). In the ITT analysis the UPPP-first strategy and the CPAP-first strategy were both composed of 75% of CPAP-treated patients at the end of follow-up. The almost equal composition of both strategies does not explain why we found no difference in improvement of QoL, because the AT analysis showed that indeed no differences existed between CPAP and UPPP treated patients, even after switching of therapy.
A limitaton of this study is that the follow-up matrix was not complete, because the study duration was limited to 3 years by the study regulations of the Investigative Medicine Committee of the Dutch Health Insurance Council. An

intake period of 2.5 years yields a preset minimal follow-up duration of 0.5 years with a maximum of 2 years (see Table 6.1).

Table 6.3. (legend on next page)

	Base-line	6 Months	p	12 Months	p	18 Months	p	24 Months	p
Somatic subscale of the Hopkins Symptom Checklist									
UPPP-first	5.4(4.2	3.8(3.9)	0.006	3.8(3.9)	NS	4.2(4.0)	NS	4.4(4.5)	0.02
CPAP-first	5.9(3.9)	4.4(3.8)	0.002	4.3(3.2)	0.05	4.1(3.2)	0.02	3.4(3.4)	0.02
p	NS	NS		NS		NS		NS	
Bradburn Affect Balance Scale									
Positive experiences									
UPPP-first	2.3(1.6)	2.8(1.6)	<0.04	3.2(1.6)	0.01	3.2(1.7)	0.02	2.7(1.8)	NS
CPAP-first	1.9(1.5)	2.8(1.7)	0.009	2.7(1.7)	<0.04	3.0(1.6)	<0.003	3.0(1.6)	0.003
p	NS	NS		NS		NS		0.02	
Negative experiences									
UPPP-first	1.4(1.4)	1.0(1.3)	NS	0.8(1.0)	0.06	1.0(1.5)	NS	1.1(1.1)	NS
CPAP-first	1.7(1.4)	1.1(1.3)	0.002	0.9(1.1)	0.002	0.9(1.1)	0.008	1.0(0.9)	0.04
p	NS	NS		NS		NS		NS	
Profile of Mood States									
Depression (1.9 ± 4.4)									
UPPP-first	5.5(6.4)	3.1(4.8)	0.07	2.5(4.5)	<0.03	4.0(6.1)	NS	3.8(5.2)	0.01
CPAP-first	6.3(5.5)	4.0(6.7)	0.005	3.2(5.4)	0.0003	2.9(4.9)	0.001	4.6(7.6)	<0.03
p	NS	0.05		NS		NS		NS	
Anger (3.7 ± 4.6)									
UPPP-first	9.1(7.4)	6.0(5.6)	0.01	6.8(5.8)	0.09	6.8(6.4)	0.03	6.9(6.5)	0.06
CPAP-first	10.3(6.1)	6.1(5.8)	<0.0001	5.5(4.8)	<0.000	5.1(4.9)	0.0003	6.6(6.8)	<0.005
p	NS	NS		0.06	1	NS		NS	
Fatigue (3.3 ± 4.4)									
UPPP-first	11.5(6.0)	6.1(5.9)	<0.0001	6.1(6.0)	0.0001	5.5(6.0)	0.0001	6.4(6.2)	0.002
CPAP-first	13.0(6.9)	6.4(7.7)	<0.0001	7.1(7.6)	<0.000	4.8(5.4)	<0.0001	4.6(5.6)	0.0004
p	NS	NS		NS	1	NS		NS	
Vigor (12.1 ± 4.5)									
UPPP-first	7.1(4.3)	9.9(4.9)	<0.002	10.8(4.8)	0.0005	10.9(3.8)	0.0001	9.6(4.5)	0.07
CPAP-first	6.3(4.5)	10.3(5.8)	<0.0001	10.4(5.6)	0.0001	9.4(5.3)	<0.003	10.3(5.4)	0.002
p	NS	NS		NS		NS		0.09	
Tension (3.6 ± 4.0)									
UPPP-first	6.6(5.5)	3.8(4.6)	0.0002	3.4(4.0)	0.001	3.9(4.3)	<0.004	4.2(3.7)	0.002
CPAP-first	7.0(4.9)	4.8(5.1)	0.0006	3.5(3.8)	<0.000	3.7(3.7)	<0.0001	3.7(5.0)	0.006
p	NS	NS		NS	1	NS		NS	

Legend to table 6.3.

The absolute scores with their standard deviation between brackets on the SOMAT, ABS and the POMS. The normative scores ± standard deviation of the POMS obtained from Wald and Mellenbergh (17), are displayed between brackets behind the title of every subscale. The level of significance (Wilcoxon signed-rank) of the improvement of every subscore is displayed in the column following every follow-up visit (vertically). The level of significance of the difference in improvement between the two strategies (Mann-Whitney U) is displayed in the last row of the corresponding sub score (horizontally). NS means not significant and no trend ($p > 0.10$).

When comparing the scores on the NHP part 1 to the recalculated norm scores of Erdman (15), all scores at base-line exceed the scores of this norm group of 98 patients by 2 to 3 times (see table 6.2.). Despite the statistically significant improvement of almost every score in the ITT, most scores remained well above the mean of this norm group. Patients in the UPPP-first and CPAP –first strategies showed a 50% improvement in energy score but still exceeded the norm value for diseased men by factor 2. At 24 months sleep score was in the healthy range in the CPAP-first strategy only. The pain score in the UPPP-first strategy remained relatively high during the entire follow-up (20.0 at 24 months). The AT results support the ITT findings. The NHP part 1 was also used by Fornas et al to evaluate QoL in untreated OSAS-patients (21). They did not use weighed scores, so our data can not be compared directly to theirs. They found that the worst perceived dimensions were energy, sleep, emotional response, which is in concordance with our findings. Meslier et al used the NHP part 1 to evaluate the QoL in 3.225 respondents of 5.339 invited OSAS-patients on CPAP treatment for at least 6 months (4). All their weighed scores were higher than our scores in the CPAP-first strategy and the CPAP therapy group, with the exception of emotional response. Their population was older (median 60 versus 49) and they found in the same study that older patients have significantly higher scores for energy, pain, sleep,social isolation ,and physical mobility and significantly lower scores for emotional respons (4). Engleman et al used the NHP part 2 in a placebo controlled trial to evaluate the effect of CPAP in 32 patients with OSAS (22). They found improved ratings for social life, sex life, and ability to carry out domestic chores.
The mean score on the SOMAT in "normals" with a mean age of 24.5 years (range 13-72) was found to be 2.1 (SD = 2.3) (16). This means that the scores on the SOMAT in our population are high and remain high after treatment, between the 80^{th} and 95^{th} percentile of the norm group of Luteijn et al. (ITT and AT). Although our population can not be compared directly to these controls, this indicates that OSAS patients are likely to experience more physical complaints than controls, even after treatment with UPPP or CPAP. As far as we know the SOMAT has never been used before to assess QoL in OSAS. The

Hopkins Symptom Checklist, of wich the SOMAT is a subscale has been complemented with psychiatric items to form the Symptom Checklist –90 revised (SCL-90) (16). This SCL-90 has been used in a study in 1993, in which Gall at all found no differences between patients with mild OSAS (Apnea/Hypopnea-index < 20) and controls (23).

The ABS has been translated and used in the Dutch situation. We were however not able to find useful normal values to compare with our results. The results show however the same tendency as the other questionnaires: a increase in positive experiences and a decrease in negative experiences in UPPP and CPAP treated patients (ITT and AT). Despite the small but statistically significant difference in the increase in positive experiences between the UPPP-first and CPAP-first strategies at 24 months, the ABS showed no consistently statistical differences between UPPP and CPAP either.

The shortened version of the validated and translated POMS was first described in 1990 by Wald and Mellenbergh (17) (see table 6.3.). In our data every domain of the POMS was considerably affected, and although the standard deviations are large, the only two domains approaching normal values after treatment were Vigor and Tension (ITT and AT). Mosko et al used the POMS to evaluate self-reported mood ratings in patients with sleep disorders in 1989 (24). Their patients showed more depression, vigor and tension than our subjects. This could well be coincidental, because the scores on anger and fatigue are similar. The effect of UPPP on the POMS scores was reported in the same study in 22 patients (24). The improvement in depression, anger and fatigue were statistically significant, the other scores showed the same improvement as in our study. Our data confirm the findings by Mosko et al. (24).

That QoL is so severely affected in untreated OSAS may be caused not only by OSAS related symptoms, but also by OSAS related sequelaea, some of which could be considered as comorbid conditions on their own. OSAS has been documented to be associated with cardiac arrhythmias, ischemic heart disease, cardiac failure, systemic or pulmonary hypertension, and stroke (25). The effects of treatment of OSAS on the associated morbidity has been shown to be variable and sometimes limited (7). This may partly be responsible for the incomplete recovery of QoL parameters. On the other hand the low improvement of desaturation parameters and surgery related complaints in UPPP treated patients and constant confrontation with the nose-mask in CPAP treated patients may have a negative effect of experienced well-being. Meslier et al demonstrated that patients with intermediate compliance to CPAP had a better perception of their health than poorly compliant patients(4). We did not objectively measure compliance to CPAP, allowing no conclusion for this aspect.

Despite the difference in the improvement of desaturation parameters between UPPP and CPAP treated patients in our study (chapter 5), we found no

difference in improvement of EDS and QoL between the two treatments. The discrepancy between objective and subjective improvement after treatment for OSAS has been reported earlier, especially in UPPP treated subjects (8-10). Several studies showed no correlation between respiratory parameters and EDS or QoL (23,26,27). Our data and the earlier studies support the hypothesis that other factors than sleep related respiratory disturbances or disruption of nocturnal sleep, are likely to contribute to the development of EDS and daytime dysfunction in patients with sleep apnea.

This is the first prospective, although uncontrolled study in a relatively large population demonstrating that QoL is severely affected in patients with OSAS, and that treatment with either UPPP or CPAP may result in an considerable improvement of QoL, but without restoring it to normal values. CPAP-treated patients showed a better respons and incidentally a subscale approached the normal values, but CPAP in general was not found to be superior to UPPP in perspective of improving QoL parameters.

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CHAPTER 7

General Discussion and Conclusions

7.1 Introduction

In the perspective of its relative high prevalence and the severity of its symptoms, OSAS must indeed be considered a major public health problem (1), that deserves expert medical attention and treatment. However, without a complete understanding of the pathogenesis and long-term effects on health outcome of sleep related breathing disorders (2), the development of effective treatment modalities, that are relatively non-invasive and well tolerated will remain difficult, and further research is therefore of paramount importance.
In this thesis we focussed on the treatment of OSAS with Uvulopalatopharyngoplasty (UPPP) and Continuous Positive Airway Pressure (CPAP), and pathogenetic aspects were studied to illustrate the limitations of surgical therapy (*chapter 2*). The main goal of our studies was to assess the treatment outcome after UPPP (*chapter 3 and 4*) and to evaluate whether the treatment of patients with OSAS caused by predominant collaps at the velo-pharyngeal level should be started with UPPP or CPAP (*chapters 5 and 6*).

7.2 Definition of Obstructive Sleep Apnea Syndrome

As described in the introduction, different respiratory parameters and thresholds are used in the literature to define OSAS. Most definitions were based on the recording techniques that were used. The definition of OSAS in this thesis is again somewhat different from the international literature and is a direct consequence of the two recording techniques we used for the diagnosis and evaluation of OSAS. Polysomnography is considered the gold standard for a definite diagnosis of OSAS (3,4), and for this reason we performed PSG in all our patients before including them in any of the described studies. PSG is however a very time-consuming procedure and is therefore impracticable for regular use during follow-up procedures. For this reason we considered several ambulatory devices, and selected the MESAM-4, which was the most practicable device available at that time. Pulse oximetry was included in both the PSG and MESAM 4 recording and the detailed data on arterial oxygen desaturation allowed calculation of the ODI from both recording modalities. ODI was obtained by including desaturations exceeding 3% from base-line caused by obstructive respiratory events only (apneas and hypopneas) when interpreting PSG and by excluding all artefacts from the oxygen saturation trace provided by the MESAM 4. All MESAM 4 recordings were scored by hand. Esnaola et al. showed that hand-scoring of MESAM 4 as a confirmation test compared to simultaneous PSG showed a specificity for the diagnosis of OSAS of 0.98 by an AHI threshold of 10, and of 0.97 by a threshold of 5 (5). Koziej et al. demonstrated that the correlation between a hand-scored ODI (MESAM 4) and a AHI (PSG) was 0.96, with AHI threshold of 10 as criterion for OSAS by

PSG. OSAS may therefore be redefined as the presence of daytime sleepiness and an ODI $\geq$ 5 or an AI $\geq$ 5, in the presence of obstructive respiratory events of at least 10 seconds in case of PSG, or "typical" desaturations combined with changes in heart rate and snoring trace in case of MESAM 4. Several studies have adressed the use of oximetry in the detection of OSAS (6), but an oxygen desaturation index (ODI) as part of the definition of OSAS has been used sparsely, and mainly for epidemiologic and screening purposes (7-9). The comparability of ODI with data from the literature may be limited, but the methodological restrictions of other definitions used must also be considered. The apnea-index (AI), apnea-hypopnea index (AHI) or respiratory distress index (RDI) are used most frequently (6). The definition of an apnea as a complete cessation of airflow though nose and mouth of at least 10 seconds is well established, as is the definition of AI as the mean number of apneas per hour of recorded sleep. A hypopnea is however poorly defined, but is obligatory to the definition of both AHI and RDI. Generally a hypopnea is described as a diminished airflow during at least 10 seconds, but due to the different recording techniques used it is rather a qualitative than a quantitative description of a respiratory event and a precise demarcation is impractical (10-12).
The use of these indices in defining OSAS and comparing the results of the enormous amount of studies published is therefore not as accurate as may be suggested. Furthermore the association of a specific AI or AHI (5,10,15, and so forth), with the development of a specific clinical picture and long-term health effects has never been established (12).

7.3 Pathogenetic Aspects and Treatment Outcome

The pathogenesis of OSAS has not been elucidated. The *Balance of Pressures Principle* (13,14), qualitatively describes the sleep related changes in ventilatory control and muscle tone that result in a disbalance of the dilatory and narrowing forces acting on the upper airway during sleep, and it is undisputed that anatomic narrowing further enhances the instability of the upper airway and contributes to the occurrence of obstructive respiratory events in OSAS. Further understanding of the relative contribution of different pathogenetic factors is important, because the available treatment modalities may have effect on a small part of the causative factors only. In *chapter 2* we assessed the quantitative contribution of dynamic and static upper airway obstruction parameters on the frequency and severity of nocturnal desaturation in heavily snoring and OSAS patients. We found that approximately 30% - 40% of the variation in ODI and maximal oxygen desaturation were explained by obstruction parameters alone. This finding suggests that the effect of surgical correction of upper airway anatomy on reducing nocturnal desaturations may be

limited. This is in concordance with the effect of UPPP on ODI in our patients, but Riley et al. demonstrated that an invasive stepwise surgical protocol, adressing the different obstruction sites of the upper airway may result in a treatment outcome comparable to the effect of CPAP in approximately 90% of patients (15-17). This observation suggests that reduction of upper airway compliance results in further stabilisation of ventilatory control. The stepwise protocol of Riley et al. is however very invasive and most patients will be treated by more conservative surgical techniques (nasal septum correction, UPPP etc), with a more limited effect on nocturnal breathing. This may especially be true for the idiopathic OSAS, in which anatomical abnormalities of the upper airway causing symptomatic apneas are not present.
The effect of CPAP is mediated by its influence on several contributive factors. The pneumatic splinting of the anatomically narrow upper airway may be most important (18,19), but CPAP also increases lung volume, alters central chemosensitivity and increases upper airway muscle activity (18-25). From a scientific standpoint CPAP should be more effective than surgery in the treatment of OSAS, and this hypothesis is supported by the literature and by our findings. We must however realise that our understanding of the pathogenesis of OSAS is still limited, and that this prevents us from developing more rationale treatment strategies that may be less cumbersome than CPAP.

7.4 The Evaluation of Treatment Strategies

UPPP and CPAP were introduced simultaneously for the treatment of OSAS (26,27). In the early nineties UPPP was still the most performed procedure (28), but CPAP is now considered the treatment of first choice, although only one prospective randomised placebo controlled trial has been performed to evaluate its effect (29-32). Untill recently it remained unresolved, whether treatment of OSAS in patients with predominant collaps of the upper airway at the velopharyngeal level should be started with UPPP or CPAP.

7.4.1 Uvulo-Palato-Pharyngo-Plasty (UPPP)

UPPP is performed to reduce redundant velopharyngeal tissue to reduce the collapsibility of the upper airway. Although the procedure has been widely accepted as a treatment modality for OSAS, there is a marked inconsistence between subjective and objective improvement of symptoms. Furthermore, there is increasing evidence that the initial response decreases over the years following treatment. Our studies confirm these general considerations. In *chapter 3* we described the treatment outcome 6 months after UPPP, and found a significant improvement of snoring (73% of patients), and daytime sleepiness

(55% of patients), but improvement of ODI was not significant. In *chapter 4* we described the long-term outcome in the same study cohort, after a follow-up period of 11 – 74 months. We found that snoring remained significantly improved (63% of patients), but that daytime sleepiness relapsed to pre-operative levels, and that ODI was not changed. Several explanations for this finding can be postulated. As described earlier the process of attribution may explain part of the initial subjective improvement (see chapter 5), and it is likely that this attribution will attenuate over the years. Considering the relative small improvement of respiratory parameters following UPPP, suggesting a minor anatomical correction only, it may well be that this procedure provides a temporary set-back or delay in the natural evolution of the syndrome and its symptomatology. Although we reperformed the Mueller manoeuver in some of our patients, we were not able to show progressive recurrence of upper airway collaps over the years following treatment, but this seems the most plausible explanation. A new finding in our long-term study was the significant better improvement of ODI after UPPP combined with tonsillectomy, compared to UPPP alone (in case tonsillectomy was already performed for other reasons). One explanation for this finding may be, that the presence of palatine tonsils reduces the upper airway aperture and further enhances collapsibility during sleep. Although this mechanism is not supported by the finding of the Mueller manoeuver, it is reflected by the higher sleep apnea severity as expressed in ODI between UPPP + TE and UPPP only patients at baseline. Removal of this causative contributing factor may itself result in better improvement of ODI, but the resection of tissue in the tonsillar fossa results in a more lateral expansion of the incision and consequently of the suture line. A more generous resection of the soft palate may therefore be complementary to the effect of tonsillectomy alone and may contribute to better treatment outcome (33). Furthermore several studies and our own results showed that improvement of ODI was related to relatively high pre-operative ODI, and since UPPP + TE patients had more severe OSAS, this mechanism may also be partly responsible (*chapter 3 and 4*).

Another serious limitation of UPPP is the almost complete absence of clinically useful pre-operative selection criteria. It is generally accepted that UPPP should not be performed in patients with high body weight, high sleep apnea severity, and significant collapse of the upper airway at any other level than the velopharynx, but a high number of treatment failures should still be accounted for. The presence of tonsillar tissue may be a useful selection criterion, but this needs further evaluation in prospective trials.

Although the effect of UPPP is seriously limited and a relapse of symptoms is likely to occur within 3 years following surgery, it can not be disputed that a small group of patients (20% - 25%) must still be considered responders on the long-term. This finding was confirmed in the analysis of the Dutch Sleep Apnea Study (see further). Twenty-three percent of patients initially treated with UPPP, did not switch to CPAP after 24 months of follow-up, and no

statistically significant differences in daytime sleepiness, quality of life and nocturnal desaturations were found between these patients and patients using CPAP.

7.4.2 Evaluation of UPPP and CPAP in two Alternative Treatment Strategies

CPAP is considered treatment of first choice in OSAS, irrespective of the level of upper airway obstruction (32). UPPP should by preference be reserved for patients with predominant collaps at the velopharyngeal level (34). UPPP and CPAP may, therefore, both be indicated for the treatment of OSAS in these patients. A single randomised prospective study comparing both treatments has never been performed.

The Dutch Sleep Apnea Study was the first prospective randomised study comparing UPPP and CPAP for the treatment of OSAS caused by predominant obstruction at the velopharyngeal level. The study was performed for the Dutch Health Insurance Council. The main goal of this study was to evaluate whether treatment in these patients should be started with UPPP or CPAP. The design of the study was based on every day clinical practice with regard to clinical work-up, diagnosis, treatment indication, and clinical follow-up. Follow-up visits were at regular intervals of six months during two years. In case of treatment failure patients could switch to the other treatment modality, and this guaranteed optimal treatment of any individual patient within the regulations of the study protocol. We performed two different statistical analyses. In the Intention-To-Treat (ITT) analysis patients starting with UPPP were compared to patients starting with CPAP, and eventual switchers from therapy remained in the original strategy. In the As Treated (AT) analysis four different treatment groups were compared: patients after UPPP only, patients on CPA only, patients on CPAP secondary to UPPP, and patients after UPPP secondary to CPAP. The results of the AT analysis are described only in the Quality of Life analysis in *chapter 6*. We defined the following end-points:

1. The number of patients improving at least one point on the 4-point daytime sleepiness scale after 6 months of follow-up following the ITT principle.
2. The number of patients improving at least one point on the 4-point daytime sleepiness scale after 12 months of follow-up following the ITT principle.

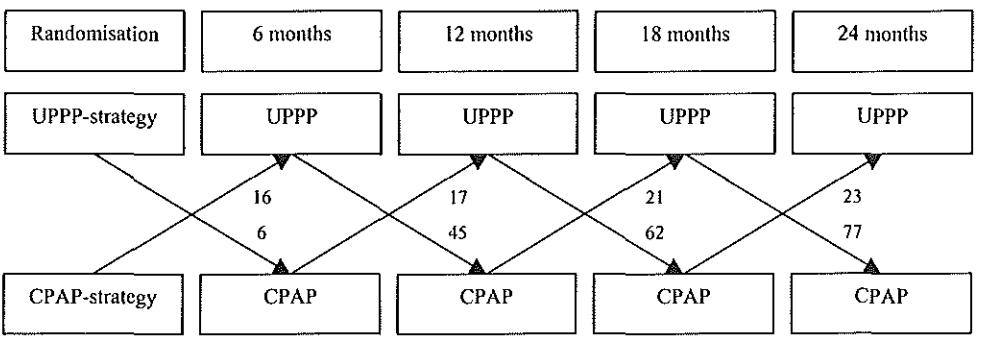
Due to the large number of switches from UPPP to CPAP and the predominant switching from CPAP to UPPP at the beginning of the follow-up period (figure 7.1), we had to consider the amount of switchers as a major end-point as well.

We therefore defined a complementary end-point:

3. The percentage of patients switching from treatment after 12 months of follow-up.

The percentage of patients switching from treatment at 6 months was not analysed, because in the UPPP-strategy switching was not allowed within 6 months after surgery. The numbers of patients at 18 and 24 months were too small for statistical analysis (*chapter 5*). Secondary end-points were differences in quality of life measures and nocturnal ODI between the two strategies.

Figure 7.1. The cumulative percentage of patients switching between treatments (see text)



Daytime sleepiness was significantly improved in both strategies, and we found no difference between the strategies considering this primary endpoint on 6 and 12 months of follow-up. Quality of life measures improved significantly in both strategies in the ITT analysis, and no consistent differences were found between UPPP-first treated and CPAP-first treated patients. The AT analysis showed the same result, but patients in the CPAP after UPPP group tended to score worse than the other three groups. We found a significant difference in the improvement of ODI in advantage of the CPAP-first treated patients at six months. At 12, 18, and 24 months the improvement of ODI was significant in both strategies, and the differences between the two strategies decreased progressively and were not statistically significant. This can be explained by the high percentage of patients treated with CPAP in the UPPP-first strategy at the later stages of follow-up. We also performed a cost-minimalisation analysis, and found that both the direct and consequential costs were significantly lower if treatment was started with CPAP. This is due to the fact that, at the end of the study 77% of patients were switched from UPPP to CPAP, compared to 23% of patients that switched from CPAP to UPPP. In both strategies an equal percentage of patients was eventually treated with CPAP, but the short-term costs of operation and hospitalisation attached to UPPP in the UPPP-first strategy, account for the difference.

When we reconsider the fact that we designed the study to allow switching from treatment in case of treatment failure, as judged by the patient or his physician,

we initiated a "self-selection" proces. This proces resulted eventually in an equal distribution of treatments in both strategies (75% of CPAP and 25% of UPPP), and as a consequence no differences should be found between these two similar groups. The analysis of the ODI provides objective evidence of the effectivity of this "self-selection"proces.
An important consideration is that minor differences in the primary end-point could be present between the two strategies, but that the power of this study may not be enough to detect it. The aspects possibly responsible for this lack of power are discussed in detail in *chapter 5*. Although we did not find any statistically significant difference with regard to the primary end-points between UPPP-first and CPAP first treated patients, this study provides enough arguments for CPAP to be considered treatment of first choice for patients with OSAS caused by collaps at the velopharyngeal level. Starting treatment with CPAP will lead to less treatment failures and to less switching of therapy. Starting treatment with CPAP results in better improvement of nocturnal oxygen saturation. Starting treatment with CPAP is cheaper, not only because it spares the initial costs of UPPP in appoximately 75% of patients, but the direct and consequential costs in CPAP treated patients, even if they decide to switch to UPPP are significantly lower. Although we found that a maximum of 23% of UPPP treated patients were good responders at the end of follow-up, we found no clinically useful pre-operative selection criteria for the identification of possible responders or possible treatment failures. This means that any individual patient has a 23% chance of long term effective treatment when offered UPPP, versus a 77% chance when offered CPAP.

7.5 Conclusions and Considerations for the Future

OSAS may have severe consequences for every individual patient with regard to nocturnal sleep and daytime functioning, and there is enough scientific evidence for the relation between OSAS and cardiovascular morbidity (1). Long-term population based prospective studies to examine the precise association between OSAS and related morbidity and mortality have still not been published, and it remains therefore unresolved whether OSAS indeed causes a decrease in public health (2). It remains therefore also unresolved whether treatment of OSAS, either surgical or by CPAP will result in a decrease in OSAS related cardiovascular morbidity and mortality, although numerous studies, and our data clearly show a decrease in daytime symptoms and stabilisation of nocturnal breathing in a substantial number of patients. It remains therefore undisputed that treatment of OSAS will result in improvement of daytime symptoms, but further research is needed to establish the association between OSAS and its treatment on sleep apnea related morbidity and mortality. This research preferably demands prospective randomised controlled trials, but it can hardly

be considered ethical to include a control group of untreated OSAS patients. Furthermore, these studies should not only consider OSAS as a public health problem and as such address public health related cost and outcome measures only, but also the long-term outcome from a more individual perspective. For the future we need to accurately detect patients with OSAS, and to treat them in specialised centres. If possible they should be included in prospective trials comparing different treatment options (conservative or surgical). Comparative evaluation of the efficacy of the different treatment modalities in perspective of symptoms and cardio-vascular sequalae, may allow us to understand long-term outcome with respect to these symptoms and long-term cardio-vascular complications.

Despite the fact that CPAP was considered treatment of first choice for OSAS by many leading investigators, it was not that commonly prescribed by physicians in the Netherlands, as it was in other countries (USA, France and Germany for example). Until recently UPPP was performed frequently, especially in patients with predominant collaps of the upper airway at the velopharyngeal level. The indication for CPAP was made with reservation, because the regulations of the Dutch Health Insurance Counsel allowed treatment with CPAP under strict preconditions only, while UPPP was refunded by the Health Insurance Companies. The Dutch Sleep Apnea Study and the recently proposed Dutch Sleep Apnea Consensus, provided sufficient scientific data and opinions of Dutch experts to warrant revision of the indications for CPAP as defined by the Dutch Health Insurance Council, and to match these to the internationally accepted standards . From now on, CPAP can be considered treatment of first choice for sleep apnea patients in the Netherlands as well.

CPAP has been shown to be very effective in reducing daytime complaints and in stabilising nocturnal breathing, but it must still be considered a cumbersome treatment for a considerable number of patients. Several studies showed indeed, that compliance to CPAP may be disappointingly low (35,36), and the American Thoracic Society stated in 1994, that the compliance may at best approach 50% (37), while acceptance may be close to 70% (38-40). This observation has several consequences. The long-term results of CPAP on daytime complaints, may not be better than that of surgery (UPPP), which seems in concordance with the results of the Dutch Sleep Apnea Study, although actual compliance to CPAP was not monitored. More research is needed to understand the mechanisms contributing to better compliance, and to evaluate new CPAP techniques and masks. Although new technologies develop rapidly, it will remain impossible to treat all OSAS patients with CPAP. Until now surgery is the only well evaluated alternative, and further research must be initiated to identify useful selection criteria for specific surgical protocols or to evaluate new surgical techniques. Our data and that of many others show that UPPP, or even more extensive surgical protocols may be effective treatment modalities. We should not deny surgery to patients who can't get used to

CPAP, simply because we do not know enough about its possibilities. Although no useful clinical criteria have been established, UPPP should merely be reserved for patients with relatively mild sleep apnea severity, predominant collaps of the upper airway at the velopharyngeal level, and who are not seriously overweighed. UPPP in combination with tonsillectomy seems to be more effective in improving subjective symptoms and nocturnal desaturation. We estimate that 20% to 25% of patients will be treated effectively with regard to snoring, daytime sleepiness, and nocturnal desaturation untill three years after surgery.

Some earlier reports emphasize the possible effect of previous surgical (UPPP) procedures on the tolerance and treatment outcome of CPAP therapy if secondarily indicated (41,42). We found however no support fot this theory, because daytime sleepiness, QoL and ODI were consistently improved in the CPAP after UPPP-therapy, and these changes were not different compared to the other treatment groups. All patients in the CPAP after UPPP-therapy group continued treatment and inspiratory pressure levels and CPAP-related complaints were not different from the CPAP-therapy group.

The data presented in this thesis can be summarised by a few short general conclusions. In any situation where UPPP and CPAP are simultaneously available for the treatment of OSAS in patients with predominant collaps of the upper airway at the velopharyngeal level, CPAP should be the treatment of first choice. The acceptance of CPAP is significantly better, and it results in less treatment failures than UPPP. The improvement of nocturnal desaturations is significantly better in CPAP treated patients, but there is no evidence for a difference in improvement of daytime sleepiness and quality of life parameters between UPPP and CPAP. Treatment with CPAP-first is less expensive than treatment with UPPP-first.

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Summary

The Obstructive Sleep Apnea Syndrome (OSAS) is characterised by repetitive obstruction of the upper airway during sleep, causing obstructive apneas, nocturnal oxygen desaturation and fragmentation of sleep (*chapter 1*). Snoring, apneas and daytime sleepiness are the cardinal symptoms of the syndrome. OSAS is related to cardiovascular morbidity and mortality. Approximately 4% of middle-aged men and 2% of middle aged women meet the criteria of OSAS, as defined by the presence of daytime sleepiness and at least 5 desaturations or apneas per hour sleep. In perspective of its prevalence, symptoms and long-term sequelae, the OSAS should be considered a major public health problem. Diagnosis and treatment of OSAS and other sleep related breathing disorders requiers a multi-disciplinary approach in sleep centers or sleep apnea centers.

The pathogenesis of OSAS has not been fully elucidated, but sleep related changes in ventilatory control, sleep related changes in upper airway muscle control, and certain aspects of the upper airway anatomy are all important contributive factors. To evaluate the relative contribution of static upper airway obstruction (purely anatomic), and dynamic upper airway obstruction (ventilatory and muscular control), we studied 53 men and 7 women with excessive snoring or OSAS (*chapter 2*). Static upper airway obstruction was assessed by cephalometry, while dynamic upper airway obstruction was assessed by Mueller manoeuvre and pulmonary function testing. Nocturnal saturation and breathing pattern were documented by polysomnography (PSG). The oxygen desaturation index (ODI) and maximal desaturation were used in the analysis. We found that only 8-13% of the variation in nocturnal desaturation parameters could be explained by static upper airway obstruction, and only 30-40% by the combination of static and dynamic obstruction parameters. As a consequence 60-70% of the variation in nocturnal desaturation must be explained by other mechanisms, indicating that sleep phase related changes in ventilatory and upper airway muscle control are more important in the pathogenesis of sleep related breathing disorders and OSAS than pure anatomic narrowing of the upper airway.

Since their simultaneous introduction for the treatment of OSAS in 1981, Uvulo-Palato-Pharyngo-Plasty (UPPP) and Continuous Positive Airway Pressure applied by a nose mask (CPAP) were the principal treatment modalities for OSAS. Studies on the short-term effect of UPPP on snoring, daytime sleepiness and nocturnal breathing parameters showed a high variability, while the long term effects of this treatment were sparsely reported. To evaluate the short-term and long-term efficacy of UPPP on improving snoring, daytime sleepiness and nocturnal desaturation, we studied 60 consecutive patients with OSAS documented by PSG (*chapters 3 and 4*). We found that more than 70% of patients reported improvement of snoring and more than 50% improvement of daytime sleepiness, six months after surgery. A

more than 50% reduction in ODI was found in 35% of patients, and 13% showed a decrease of ODI below 5 after the same period of six months. After 11 to 74 months of follow-up in 58 of the original 60 patients, we found that snoring remained improved in 63%, daytime sleepiness in 38%, but no improvement of ODI. After comparing the daytime sleepiness scores to the pre-operative scores, we found that these scores showed a relapse to base-line scores. An additional finding in the long-term study (*chapter 4*) was that the outcome was significantly better after UPPP in combination with tonsillectomy, compared to UPPP alone. No other pre-operative criteria with respect to treatment outcome were found. We concluded that the effect of UPPP is limited, but that approximately 20% of patients was treated effectively in the long-term. These patients can however not be identified pre-operatively.

An increasing number of studies reported the effect of CPAP on daytime symptoms and nocturnal breathing pattern, and although no prospective randomised trial was ever performed, CPAP became the treatment of first choice. UPPP was however still considered a treatment option for patients with OSAS caused by predominant collaps of the upper airway at the velopharyngeal level. UPPP was performed frequently in the Netherlands, while the use of CPAP was severely restricted to the guidelines of the Dutch Health Insurance Council. We performed a randomised prospective trial using the Intention To Treat (ITT) principle to compare two strategies for the treatment of OSAS in patients with predominant collaps at the velopharyngeal level (*chapter 5*). In the first strategy the treatment was started with CPAP, and in the second strategy with UPPP, with the possibility to switch to the other treatment modality in case of treatment failure. We evaluated which strategy resulted in better improvement of daytime sleepiness, quality of life, and nocturnal desaturations. We also performed a cost-minimalisation analysis. 125 Patients were included between November 1992 and May 1995. Follow-up ranged from 6 to 24 months. At the end of follow-up 77% of UPPP-first patients were switched to CPAP and 23% CPAP-first patients were switched to UPPP. At the end of follow-up, 77% of the patients in both strategies were treated with CPAP. We found no statistical significant differences in improvement of daytime sleepiness or quality of life. CPAP-first strategy resulted in better improvement of nocturnal desaturation at six months, but due to the switching to the other treatment modality, the improvement of ODI was eventually equal in both strategies. Although some reports suggested that the effect of CPAP was influenced negatively by prior UPPP, we found no significant differences between patients in the CPAP after UPPP treatment group and the other patients. The mean direct costs and the cumulative consequential costs were significantly higher in the UPPP-first strategy. This was the first prospective randomised trial comparing UPPP and CPAP for the treatment of OSAS, and the results support the international consensus that CPAP is the treatment of first choice for OSAS in patients with predominant velopharyngeal obstruction.

We performed a separate analysis of Quality of Life parameters (QoL) in the same patient group (*chapter 6*). The aims of this study were to evaluate Quality of Life (QoL) before and after treatment of OSAS and to assess the differences in changes in QoL between UPPP and CPAP treated patients. The QoL measures were compared to norm values, both before and after treatment to describe the impact of OSAS on QoL and the clinical relevance of changes in QoL. QoL was assessed in a generic way with the Dutch translated and evaluated versions of the Nottingham Health Profile part 1 (NHP part 1), and in a domain specific way, focussing on somatic and psychological well-being with the Somatic subscale of the Hopkins Symptom Checklist (SOMAT), the Bradburn Affect Balance Scale (ABS) and the shortened Profile of Mood Scale (POMS) in a reliable and validated Dutch versions. We found that the base-line scores on all subscales of the NHP part 1, SOMAT, ABS, and POMS were in the range of diseased to severely diseased norm groups. In the ITT analysis a statistically significant improvement was found on almost all subscales, but mean scores were still in the diseased range. The overall comparison of the UPPP first and CPAP first treated patients showed no statistically significant differences in improvement of QoL. CPAP first treated patients however, tended to show a better respons. In the AT analysis the differences between UPPP, CPAP, CPAP after UPPP, and UPPP after CPAP were not significant. These results show that QoL is severely affected in patients with OSAS, and that treatment with UPPP or CPAP results in a considerable improvement, but without restoring QoL to normal values.

The studies described in this thesis allow the following conclusions. In any situation where UPPP and CPAP are simultaneously available for the treatment of OSAS in patients with predominant collaps of the upper airway at the velopharyngeal level, CPAP should be the treatment of first choice. The acceptance of CPAP is significantly better, and it results in less treatment failures than UPPP. The improvement of nocturnal desaturations is significantly better in CPAP treated patients, but there is no evidence for a difference in improvement of daytime sleepiness and quality of life parameters between UPPP and CPAP. Starting treatment with CPAP is less expensive than starting treatment with UPPP.

Samenvatting

Het Obstructief Slaapapneusyndroom (OSAS) wordt gekenmerkt door herhaaldelijke obstructie van de bovenste luchtweg tijdens de slaap, waardoor onderbreking van de ademhaling (apneus), zuurstofdesaturaties en fragmentatie van de slaap ontstaan (*hoofdstuk 1*). De belangrijkste symptomen van het OSAS zijn snurken, apneus en slaperigheid overdag. Er is een verband tussen OSAS en het ontstaan van cardio-vasculaire ziekten. Als we het OSAS definiëren als de aanwezigheid van slaperigheid overdag, gecombineerd met de aanwezigheid van 5 desaturaties of obstructieve apneus per uur slaap, dan voldoet ongeveer 4% van de mannen en 2% van de vrouwen op middelbare leeftijd aan deze diagnose. Vanwege deze hoge prevalentie, de symptomen en de lange termijn complicaties, moet het OSAS als een probleem voor de volksgezondheid beschouwd worden. Het stellen van de diagnose en de behandeling van het OSAS, alsmede dat van andere slaap gerelateerde functiestoornissen, verdient een multi-disciplinaire benadering in ziekenhuizen met ervaring op dit gebied.

De pathogenese van het OSAS is nog niet opgehelderd, maar slaap gerelateerde veranderingen in de controle van de ademhaling, slaap gerelateerde veranderingen in de controle van de spieren van de bovenste luchtweg en bepaalde anatomische factoren spelen alle een rol. Om de relatieve bijdrage van deze statische (anatomische) en dynamische (controle ademhaling en spieren) obstructie te evalueren, hebben we 53 mannen en 7 vrouwen bestudeerd (*hoofdstuk 2*). De statische obstructie van de bovenste luchtweg werd vastgesteld middels X-cephalometrie en de dynamische obstructie middels de Müllerse maneuvre en longfunctie onderzoek. De zuurstofsaturatie en het ademhalingspatroon werden geevalueerd met polysomnografie (PSG). De zuurstofdesaturatie-index (ODI) en de maximale desaturatie werden in de analyse gebruikt. We vonden dat slechts 8-13% van de variatie in nachtelijke desaturatie verklaard kon worden door statische luchtweg obstructie, en slechts 30-40% door de combinatie van statische en dynamische luchtweg obstructie. Dit betekent dat ongeveer 60-70% van de variatie in nachtelijke desaturatie door andere mechanismen verklaard moet worden en dat slaap gerelateerde veranderingen in de regulatie van de ademhaling en controle van de spieren van de bovenste luchtweg meer bijdragen aan het ontstaan van slaap gerelateerde ademhalingsstoornissen en OSAS, dan zuiver anatomische factoren.

Sinds de gelijktijdige introductie van de Uvulopalatopharyngoplastiek (UPPP) en de Continue Positieve Luchtdrukbehandeling (CPAP) voor de behandeling van OSAS in 1981, werden beide methoden veelvuldig toegepast. Onderzoeken naar de korte termijn resultaten van UPPP op snurken, slaperigheid overdag en nachtelijke ademhaling, lieten veel variatie zien, terwijl er nog nauwelijks onderzoek was gedaan naar de resultaten op langere termijn. Om zowel het effect van UPPP op de korte als langere termijn te evalueren, hebben we 60

patiënten met middels polysomnografie vastgesteld OSAS bestudeerd (*hoofdstukken 3 en 4*). We vonden dat 6 maanden na de operatie meer dan 70% van de patiënten een verbetering van snurken en slaperigheid overdag rapporteerde. Meer dan 50% reductie in ODI was bereikt in 35% van de patiënten, en 13% liet een afname van ODI zien tot onder de 5 per uur. Na 11 tot 74 maanden follow-up van 58 van deze 60 patiënten, vonden we in de groep, dat snurken verbeterd bleef in 63%, slaperigheid in 38%, maar dat de verbetering in ODI was verdwenen. Na vergelijking van de slaperigheidsscores met de pré-operatieve scores, bleek de slaperigheid overdag weer even ernstig als voor de operatie. Een opvallende bevinding bij de lange-termijn studie (*hoofdstuk 4*), was dat het resultaat van UPPP gecombineerd met een tonsillectomie (TE), significant beter was dan het resultaat van UPPP zonder TE. Andere mogelijke pré-operatieve selectiecriteria hebben we niet gevonden. We concludeerden dat het effect van UPPP gering was, maar dat ongeveer 20% van de patiënten ook op de langere termijn effectief behandeld was. Deze patiënten konden pré-operatief niet geselecteerd worden.
Een toenemend aantal onderzoekers rapporteerde het effect van CPAP op de symptomen en het nachtelijke ademhalingspatroon van het OSAS, en ondanks het feit dat er geen prospectieve gerandomiseerde onderzoeken hadden plaats gevonden, werd CPAP de behandeling van eerste keus. UPPP werd echter nog steeds als een optie voor behandeling beschouwd van patiënten met een OSAS veroorzaakt door collaps ter hoogte van het zachte verhemelte. In Nederland werd UPPP vaak uitgevoerd, terwijl het voorschrijven van CPAP sterk aan banden werd gelegd door de richtlijnen van de Ziekenfondsraad. Om na te gaan welke plaats CPAP kon innemen naast UPPP voor de behandeling van OSAS bij patiënten met collaps op het nivo van het zachte verhemelte, hebben we in samenwerking met de Nederlandse Ziekenfondsraad, een gerandomiseerd prospectief onderzoek uitgevoerd, waarbij twee strategieën vergeleken werden (*hoofdstuk 5*). In de eerste strategie werd de behandeling gestart met UPPP (UPPP-eerst strategie), en in de tweede met CPAP (CPAP-eerst strategie), waarbij de mogelijkheid bestond om in het geval van onvoldoende resultaat van behandeling te wisselen. We hebben geëvalueerd welke strategie resulteerde in grotere verbetering van slapergheid overdag, kwaliteit van leven en nachtelijke desaturaties, waarbij we ook een kosten-minimalisatie analyse uitgevoerd hebben. Tussen november 1992 en mei 1995 werden 125 patiënten in het onderzoek opgenomen. Follow-up vond plaats op 6, 12, 18 en 24 maanden na start van de behandeling. Aan het eind van het onderzoek waren 77% van de patiënten uit de UPPP-eerst strategie op CPAP overgegaan, in vergelijking met 23% uit de CPAP-eerst strategie die op UPPP overgingen. Uiteindelijk werd in beide strategieën dus 77% van de patiënten met CPAP behandeld. We vonden geen verschil in verbetering van slaperigheid overdag of kwaliteit van leven. De CPAP-eerst strategie resulteerde in een significant grotere verbetering van de ODI na 6 maanden follow-up, maar door het toenemend aantal patiënten dat

van UPPP naar CPAP wisselde (maar voor de analyse dus in de UPPP-eerst strategie bleef) verdween dit verschil in de loop van het onderzoek. We vonden geen verschillen tussen patiënten die met CPAP na UPPP behandeld werden en de andere patiënten, dit in tegenstelling tot de suggestie van andere onderzoekers, dat het gebruik van CPAP nadelig beïnvloed werd door eerdere UPPP. Zowel de directe als de indirecte kosten hoger waren in de UPPP-eerst strategie.

In een aparte analyse hebben we aspecten met betrekking tot de kwaliteit van leven in deze patiëntengroep geëvalueerd (*hoofdstuk 6*). Het doel van deze studie was de kwaliteit van leven voor en na behandeling van het OSAS en de verschillen tussen UPPP en CPAP te evalueren. De kwaliteit van leven scores voor en na behandeling werden vergeleken met genormeerde scores, om de invloed van OSAS op kwaliteit van leven en de klinische relevantie van eventuele verbetering te beschrijven. De kwaliteit van leven werd op een generieke wijze geëvalueerd middels de in het Nederlands vertaalde en gevalideerde versie van de Nottingham Health Profile part 1 (NHP part 1), en op een domein specifieke wijze middels de Somatische subscale van de Hopkins Symptom Checklist (SOMAT), de Bradburn Affect Balance Scale (ABS) en de verkorte versie van de Profile of Mood States (POMS). We vonden na vergelijking met de genormeerde scores, dat de uitgangsscores (voor behandeling) op alle schalen van de NHP part 1, SOMAT, ABS en de POMS in het bereik van ziek tot ernstig ziek lagen. Na behandeling waren bijna alle subscores significant verbeterd, maar nog steeds in het bereik van ziek. We vonden geen statistisch significante verschillen tussen de UPPP-eerst en de CPAP-eerst strategie, maar er was een tendens tot grotere verbetering in de CPAP-eerst strategie. In een subgroep analyse, waarbij CPAP, UPPP, CPAP na UPPP en UPPP na CPAP behandelde patiënten vergeleken werden, vonden we ook geen verschillen. Deze gegevens laten zien dat de kwaliteit van leven ernstig aangedaan is bij OSAS-patiënten en dat behandeling wel leidt tot een aanzienlijke verbetering, maar niet tot een "normalisering" hiervan.

In hoofdstuk 5 en 6 beschreven we de resultaten van het eerste prospectief gerandomiseerde onderzoek, waarbij UPPP en CPAP direkt vergeleken werden. De resultaten bevestigen de al langer internationaal heersende consensus, dat CPAP de behandeling van eerste keuze dient te zijn voor patiënten met het OSAS veroorzaakt door collaps van de luchtweg op het nivo van het zachte verhemelte. De beschreven onderzoeken leiden tot de volgende conclusies. In elke situatie waar zowel UPPP als CPAP beschikbaar zijn voor de behandeling van patiënten met het OSAS en collaps van het zachte verhemelte, verdient CPAP de absolute voorkeur. CPAP wordt beter verdragen, resulteert in minder wisselingen van therapie en resulteert in grotere verbetering van nachtelijke saturatie. Er zijn geen aanwijzingen dat CPAP ook resulteert in grotere verbetering van slaperigheid overdag of kwaliteit van leven. Het is goedkoper om de behandeling te starten met CPAP, dan met UPPP.

List of Abbreviations

ABS	: Bradburn Affect Balance Scale
AHI	: Apnea-Hypopnea Index
AI	: Apnea Index
AT	: As Treated (in statistical analysis)
BIPAP	: Bi-level Positive Airway Pressure
BMI	: Body Mass Index (kg/m^2)
COPD	: Chronic Obstructive Pulmonary Disease
CPAP	: Continuous Positive Airway Pressure
DI	: Desaturation Index
EDS	: Excessive Daytime Sleepiness
EEG	: Electro-Encephalo-Graphy
EMG	: Electro-Myo-Graphy
EOG	: Electro-Oculo-Graphy
ITT	: Intention To Treat (in statistical analysis)
LAUP	: Laser Assisted Uvulo-(Palato-Pharyngo) Plasty
MESAM-4	: Madaus Electronic Sleep Analysing machine type 4
MPH	: distance between Mandibular Plane and Hyoid
MSLT	: Multiple Sleep Latency Test
MSP	: collapse by Mueller manoeuver at the Soft Palate
MTB	: collapse by Mueller manoeuver at the Tongue Base
NHP	: Nottingham Health Profile
NREM	: Non-Rapid Eye Movement sleep
NS	: Not statistically Significant
ODI	: Oxygen Desaturation Index
OSAS	: Obstructive Sleep Apnea Syndrome
PAS	: Posterior Airway Space
PEF	: Peak Expiratory Flow
PIF	: Peak Inspiratory Flow
POMS	: Profile of Mood States
PSG	: Polysomnography
QoL	: Quality of Life
RDI	: Respiratory Distress Index
REM	: Rapid Eye Movement sleep
SD	: Standard Deviation
SOMAT	: Somatic subscale of the Hopkins Symptom Checklist
SPD	: Soft Palate Diameter
SPL	: Soft Palate Length
SRBD	: Sleep Related Breathing Disorder
TE	: Tonsillectomy
UARS	: Upper Airway Resistance Syndrome
UPPP	: Uvulo-Palato-Pharyngo-Plasty

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Henk

Curriculum Vitae

De schrijver van dit proefschrift werd op 26 december 1964 geboren in Enschede. Hij volgde zijn middelbare schoolopleiding aan het "Revius Lyceum" te Doorn, alwaar hij in 1983 het VWO (Gymnasium) diploma haalde. In 1984 begon hij met de studie geneeskunde aan de Erasmus Universiteit te Rotterdam. In oktober 1991 haalde hij zijn arts-examen. Tot medio december 1991 is hij werkzaam geweest in de functie van arts bij de Rotterdam Medical Research Foundation. Van december 1991 tot eind juni 1992 was hij AGNIO-neurologie (Assistant Geneeskundige Niet In Opleiding) in het Onze Lieve Vrouwe Gasthuis te Amsterdam. Sinds 1 juli 1992 is hij werkzaam aan de afdeling neurologie van het Academisch Ziekenhuis Rotterdam. Na een korte periode van 3 maanden als AGNIO, is hij tot februari 1996 bezig geweest met de in dit proefschrift beschreven onderzoeken. In deze periode is hij nauw betrokken geweest bij de diagnostiek en behandeling van patiënten met slaap gerelateerde functiestoornissen. Sinds 1 februari 1996 is hij in het Academisch Ziekenhuis te Rotterdam in opleiding tot neuroloog (opleider Prof. Dr. F.G.A. van der Meché).