A tailor made approach to obstructive sleep apnea
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Discussion
Obstructive sleep apnea (OSA) is the most prevalent sleep disordered breathing disorder (SDB). Interest increased once the high prevalence of OSA and the association between OSA and cardiovascular disease became apparent.\textsuperscript{1} An exponential increase has taken place in peer-reviewed publications on OSA. A search in the electronic bibliographical database Pubmed leads to more than 1600 research publications on OSA which were published in the year 2012, whilst in 1992, there were just over 200.\textsuperscript{2} Based on the latest medical research, evidence based recommendations have been formulated for the evaluation, diagnosis, treatment and follow-up of OSA patients, although many aspects of sleep medicine practice do not rely on level I or II evidence.\textsuperscript{3-12} Since, OSA is a relatively new disease entity, much remains to be discovered and improved and many areas of the field remain controversial or unproven, especially concerning treatment of OSA patients.\textsuperscript{13} Even though continuous positive airway pressure (CPAP) has the firmest evidence base in the treatment of OSA, a growing body of evidence is becoming available, supporting the practice of other treatment modalities, especially mandibular advancement devices (MADs), weight loss, positional therapy (PT) and sleep surgery. The treatment armamentarium for OSA is extensive.\textsuperscript{14}

Currently, the approach to treating OSA is steadily moving from a CPAP-centred one-size-fits-all approach to individualised treatment of upper airway obstruction during sleep.\textsuperscript{1} The latter being the keynote of this thesis.

**A TAILOR MADE APPROACH TO OSA**

**OSA TREATMENT SELECTION**

Choice of treatment depends on patient characteristics, OSA severity, sleep position dependence, co-morbidity and patient preference for instance.

**PATIENT CHARACTERISTICS**

Important patient characteristics are craniofacial and upper airway soft tissue abnormalities, such as an abnormal maxillary or short mandibular
size, tonsillar hypertrophy and adenoid hypertrophy. Further important patient characteristics include modifiable risk factors such as intoxications (including tobacco, alcohol and other recreational drug use) and medication (sedative use, in particular). In this thesis we paid particular attention to the patient characteristic overweight, the strongest risk factor associated with OSA. An increased body mass index (BMI) is not only associated with an increased prevalence of OSA, it is also related to a decreased surgical success rate and MAD failure.\textsuperscript{15-19}

In chapter 2 we investigate various associations between patient characteristics and certain patterns and configurations of upper airway collapse as assessed by drug-induced sleep endoscopy (DISE). Our observations suggest that an increased BMI is related to a concentric collapse of the upper airway as assessed by DISE; in particular a complete concentric velar collapse. In chapter 3 we test the hypothesis that certain DISE findings can predict the outcome of upper airway surgery in OSA patients. We demonstrate that the presence of a complete concentric collapse at velum level is an independent predictor of upper airway surgery failure. Although further research is needed, these results dissuade the practice of current forms of palatal surgery in patients with a complete concentric collapse of the palate or an increased BMI.\textsuperscript{15, 20}

In overweight patients with OSA, even modest weight loss can be effective in reducing OSA severity.\textsuperscript{21-23} Unfortunately, losing weight is particularly tasking in patients with OSA. Daytime hypersomnolence, an important symptom of OSA, reduces the motivation for physical activity and dieting.\textsuperscript{24} Secondly, OSA is thought to induce weight gain. Sleep deprivation and intermittent hypoxia may cause impaired glucose metabolism, hyperphagia and imbalances of leptin, ghrelin and orexin levels.\textsuperscript{25, 26} Therefore, on the whole, conservative treatment fails more often in obese patients with OSA. In such patients bariatric surgery (BS) can be considered. BS is not only the most effective treatment modality in obese patients to lose weight, producing durable weight loss, it is also known to have a positive effect on comorbidities.\textsuperscript{27, 28} Patients with OSA are particularly vulnerable during anesthesia and sedation and at an increased risk of developing respiratory and cardiopulmonary
complications postoperatively.\textsuperscript{29} These risks can be decreased by adequate management of the OSA perioperatively. In chapter 4 we show that the prevalence of OSA nears 70\% in patients undergoing BS. More than 40\% of these patients have severe OSA. Our results are consistent with similar studies.

We also demonstrate that the BMI, neck circumference (NC) and Epworth sleepiness scale (ESS) are inadequate predictors of OSA and contend that polysomnography (PSG) is an essential component of the preoperative workup of patients undergoing BS to ensure adequate perioperative management of OSA to prevent OSA-related complications of BS.

In the subsequent chapter we confirm the significant, marked improvement and even remission of OSA following BS in obese patients, as measured by PSG. The gross majority of patients reported a significant decrease in apnea hypopnea index (AHI) and other OSA parameters following BS, but the mean AHI after BS is consistent with moderately severe OSA. Patients with preoperative mild disease were more likely to be “cured” than those with a preoperative severe disease. Studies have shown that weight loss following BS, is rapid in the first few months, but it can take at least 1 year or more to reach the final result.\textsuperscript{30} Weight loss continues albeit at a slower rate over the next 6 months.\textsuperscript{27} The same pattern can be observed when studying the effect of BS on OSA. BS initiates dramatic improvement of clinical and sleep parameters during the first 7 months, thereafter improvement continues albeit at a slower rate. Physicians should bear in mind that sleep and clinical parameters will most probably have improved significantly 6 months after surgery, but a continuation of reduction in the severity of OSA and improvement of the success rate can be expected thereafter. Based on these results, in patients undergoing BS, we recommend follow-up PSG at 6 months and in the case of persistent disease, again at 12 months after surgery to check for residual disease and if necessary retrimination of CPAP, which may lead to higher treatment compliance.
OSA SEVERITY

In chapter 2 we show that visualization of multilevel obstruction sites, during DISE, was significantly associated with a higher AHI, being the very reason for the severity of the OSA. Consequentially if surgery is considered in patients with a raised AHI, adequate assessment of all sites of obstruction is compulsory to compose a befitting multi-level surgical plan. Such procedures are often more demanding and surgical success may be harder to achieve. Secondly as a rule, it is easier to reach surgical success in patients with a low AHI. A reduction of a mere 10 points is needed to reach Sher’s surgical success criteria (a postoperative reduction of the AHI by 50% and to below 20) in a patient with an initial AHI of 20, while a far larger decrease would be necessary in a patient with an AHI of 60. A complete collapse and tongue base collapse were also more pronounced in patients with a higher AHI. Similar conclusions were made by Steinhart et al who report that patients with high AHI values exhibited a more pronounced collapsibility at the base of tongue. In chapter 3 we show that a complete tongue base collapse proved to be a significant determinant of failure of upper airway surgery.

POSITION DEPENDENCE

In studies from Israel and the Netherlands a remarkable steady 56% of OSA patients has position dependent OSA (POSA) defined as a difference of 50% or more in apnea index between supine and non-supine positions. Studies suggest that on average patients with POSA have a lower BMI and a lower AHI than non-positional OSA patients. Results displayed in chapter 2 show that visualization of a base of tongue obstruction or epiglottis obstruction, during DISE is more common in patients with POSA in comparison to patients with OSA. Supporting this observation, various studies have shown that MADs are more effective in patients with positional OSA than in patients without positional OSA.

Over time various techniques have been described to prevent patients from adopting the supine position as presented in the literature review on POSA and its therapy (chapter 6). Despite a positive effect on the AHI, ineffectiveness, backache, discomfort and no improvement in sleep
quality or daytime alertness have been responsible for poor compliance and the subsequent disappointing long-term results of PT. Therefore, until recently, PT was not common practice. Recent developments have seen the introduction of a new generation of PT, which successfully prevents patients from adopting the supine position without negatively influencing sleep efficiency.\(^{37}\) It is to be expected that PT will gain momentum in the scope of OSA treatment as studies emerge suggesting that the latter is effective, well tolerated, does not disturb sleep, is reversible, has negligible side effects and all at acceptable costs.

**GENERAL DISCUSSION**

CPAP has the firmest evidence base in the treatment of OSA. In many countries if at all, only costs of CPAP are reimbursed or machine rental is subsidised by insurance companies.\(^{38,39}\) However, despite the efficacy of CPAP, it is a clinical reality that the use of CPAP is not suited for every patient. Patients seem to either tolerate the device well or not at all—a bimodal distribution.\(^{40}\) Studies have shown that 29%-83% of patients are non-adherent, when adherence is defined as at least 4 hours of CPAP use per night.\(^{41}\)

A growing body of evidence is becoming available, supporting the practice of other treatment modalities, especially mandibular advancement devices (MADs), weight loss, positional therapy (PT) and sleep surgery. The most commonly performed surgical procedure for OSA is uvulopalatopharyngoplasty (UPPP). In non-morbidly obese subjects, a fully visible soft palate associated with large tonsils is considered predictive of a high probability of success for UPPP with tonsillectomy.\(^1,42\) Unfortunately UPPP is often misused as the first line of surgical therapy for OSA, without adequate assessment of obstruction site(s) and regardless of predictive factors such as obesity.\(^{43}\) As a result, an isolated UPPP is often unsuccessful in treating OSA, especially in badly selected patients.

It is intuitively obvious that by directing surgical procedures toward obstruction-specific structures, surgical outcomes will improve.\(^{44}\) DISE not only uniquely offers a dynamic evaluation of the upper airway during
conditions that ideally mimic natural sleep but also enables visualization of specific structures that contribute to upper airway obstruction. Several studies have examined its safety, feasibility, validity, and reliability.\textsuperscript{31, 44-47}

Until recently, data associating DISE results with the outcome of surgical procedures were sparse and inconclusive because they failed to determine any independent predictive value of DISE features for surgical results.\textsuperscript{48-50} Our observations, as presented in this thesis, suggest that when surgery is concerned, a site-specific approach is valuable, while taking pattern and degree of collapse into consideration as well as keeping predictors of treatment outcome into consideration.\textsuperscript{15}

Research in well-selected patients with obvious anatomical correctable features suggests that surgery can be a viable alternative to CPAP therapy. However, comparison of the efficacy of the various treatment modalities is confused by the fact that different definitions of successful therapy are being used.

However, the effectiveness of conservative treatment regarding the reduction of AHI depends both on its impact on airway obstruction and compliance. Presently the second aspect is often overlooked. Currently, when reporting on treatment effectiveness of conservative treatment, the reduction in AHI whilst using CPAP in laboratory situations is documented. An artificial compliance of 100\% is assumed. It is however common knowledge, that a majority of patients are not adherent to the treatment during 100\% of the total sleep time under everyday, non-laboratory conditions.\textsuperscript{41} In this thesis (chapter 7 and 8) we suggest that OSA treatment effects on the AHI should no longer be reported under conditions of artificial compliance only, but in consideration of the individual compliance to the treatment. This is of particular importance when different treatment options are compared. Compliance can objectively be measured in CPAP and until recently also in MAD and PT treatment.\textsuperscript{51} We advocate that using a mean AHI in CPAP therapy is more realistic than using arbitrary compliance rates, which in fact hide insufficient reductions in AHI. Current trends define compliance as 4 hour/night as an average over all nights observed. The mean AHI can
be calculated based on the treatment period and the hours of use of the device as described in chapter 7. The first papers, taking compliance into consideration when reporting on the efficacy of either MAD or CPAP, have been published. In a recent study, the higher reported compliance to MADs translated into a similar adjusted effectiveness in comparison to CPAP, when compliance was taken into account. By using the mean AHI over the whole night, instead of the mean AHI while using CPAP and aiming at a mean AHI ≤ 5, the percentage of total sleep time (TST) during which CPAP should be used, increases as a result. Considering that 29% to 83% of patients are non-adherent and use their CPAP less than 4 hours per night, one can conclude that a goal of a mean AHI ≤ 5, for both surgical and non-surgical therapy, is rarely achievable. Have we set the bar to high? It remains questionable whether a patient is only cured when the AHI falls below 5. The point at which the AHI becomes harmful remains unclear. He et al reported an acceleration of harm when the AHI rises above 20 -25.

Still in most countries only costs of CPAP are reimbursed, if at all, or machine rental is subsidised. Even more appalling is that in some countries such as Austria, Belgium, Cyprus, Greece, Ireland, Latvia, Lithuania, Slovakia and the UK (if undertaken within the National Health Service), no or only partial reimbursement is made available for sleep testing for OSA. In this day and age, it seems that insurance companies dictate healthcare and clinical practice. Each country has its own internal guideline in mandating at which severity OSA with or without the presence of comorbidities, coverage is provided. The economic burden of OSA (health costs, lost productivity, accidents, loss of life quality) is substantial, accounting for billions of dollars per year and is expected to increase. Unfortunately, governments, transportation agencies and insurance companies pay insufficient attention to the economic impact of untreated OSA, the benefits of therapy and the complete armamentarium of treatment options. Fortunately, studies have demonstrated that treating OSA is not only cost-effective but may even be cost saving therefore encouraging insurance companies to consider cost coverage of OSA diagnosis and treatment. In the Netherlands we have the unique situation that
both diagnosis and various forms of treatment are subsidised by insurance companies, depending on OSA severity for instance, thereby facilitating research. An example for other countries.

To further restrain the economic impact of untreated OSA, it is important to recognize the significance of patient education in OSA. Not only is it imperative to educate the general population on the symptoms of OSA and the high prevalence of OSA, especially in the overweight population, but patients must also be aware of the risks and need for appropriate treatment and consequently the importance of follow-up PSG after initiation of treatment, as to encourage compliance.

To ensure optimal treatment, a tailor made approach to OSA is imperative, as advocated in this thesis. Choice of treatment should depend on patient characteristics, OSA severity, sleep position dependence, comorbidity and patient preference for instance. Behaviour modification is indicated for all patients with a modifiable risk factor. As shown in this thesis it is particularly interesting to address the risk factors overweight and position dependence. On prescribing CPAP therapy, instead of a one-size-fits-all approach, the latter must be tailored to each individual patient to optimize compliance and therapeutic benefit. When surgery is concerned, a site-specific approach is advised, while taking pattern and degree of collapse into consideration as well as keeping predictors of treatment outcome into consideration.\textsuperscript{15}

**STRENGTHS AND WEAKNESSES OF THIS THESIS**

Many chapters in this thesis focus on unraveling predictors of surgical treatment outcome, therefore advancing practice of individually tailored treatment. Until the publication of the research as published in this thesis, data associating DISE results with the outcome of surgical procedures was sparse and inconclusive, failing to determine any independent predictive value of DISE features for surgical results. Our results help us improve our understanding of the pathogenesis of OSA, as well as assisting the sleep surgeon to tailor surgery for the patient.
Despite several studies having examined the safety, feasibility, validity, and reliability of DISE, DISE antagonists argue that drug-induced sleep is not equivalent to natural physiologic sleep. Ideally sleep endoscopy would be performed during natural sleep, a tedious and challenging procedure, rarely applied. Although we have the impression that surgical success rates in patients selected by DISE are better than average, this has to be confirmed in more studies. It would be particularly interesting to compare DISE in randomized controlled setting with other evaluation techniques: is the success rate better? Are the locations of treatment recommendations given after DISE different in comparison to other treatment modalities? In a recent study by Eichler et al aimed at detecting whether locations of treatment recommendations given after DISE are different to those made after clinical basic ENT (ear, nose, throat) examination (CBE), nearly two-thirds (only surgical recommendations) to three-quarters (including MAD) of the patients with OSA examined by CBE showed at least one changed treatment recommendation after DISE. This suggests a relevant impact of DISE on treatment planning, however the proof that the changed treatment recommendation after DISE would be more effective remains to be studied.

In retrospect, the study setup in chapter 2 could have been improved significantly to increase the reliability of the results, namely the small study population, un-blinded study set-up and the heterogenous methods of sedation. Larger, blinded studies using uniform sedation methods can generate more accurate associations. The main weaknesses of chapter 3 were the retrospective nature of the study. Further larger-scale studies are needed to prospectively confirm the performance of the aforementioned variables in predicting surgical outcome. Particular attention should be paid to diagnostic modalities in identifying suitable candidates for the various treatment methods.

In this thesis we investigated the BS population. Unfortunately our study suggests that clinical predictors cannot reliably predict the presence of OSA and that a PSG is mandatory in the preoperative work-up of patients undergoing BS. The main advantage of our study is that all patients being evaluated for BS underwent a PSG regardless of history or clinical findings.
In the follow-up study ideally all patients who underwent a preoperative PSG and BS would have been invited for a PSG 6 months postoperatively regardless of the presence or absence of OSA preoperatively. Likewise regardless of the outcome of the first postoperative PSG, ideally all patients would have been invited for a second PSG 12 months postoperatively.

It can be questioned whether patients with a preoperative AHI below 5, continue to maintain an AHI below 5 postoperatively. For example, some patients may have gained weight with a consequent increase in AHI. Nonetheless, these data clearly objectify the significant, marked improvement and even remission of OSA following BS in obese patients, as measured by PSG. In this series of patients with OSA, BS initiates dramatic improvement of clinical and sleep parameters during the first 7 months, which continues at a slower rate over the next 10 months. To our best knowledge this is the first paper studying the effect of BS on OSA at 2 intervals postoperatively. In the future it would be interesting to perform a randomized-controlled trial, comparing BS versus conservative weight loss and the effect on OSA. In logistic regression models age, pre-operative BMI and weight, were inadequate predictors of cure and surgical success (Sher’s criteria) at both measurement intervals.

In chapter 7 and 8 we challenge definitions of treatment success in OSA. These chapters provide evidence that the suboptimal use of “highly effective CPAP treatment” can be compared with the 100% of the TST effect of “sub-therapeutic” surgical treatment effect. Furthermore, we argue that treatment adherence must be taken into account especially when conservative treatments like CPAP and MAD are compared to surgical interventions.

A number of caveats need to be noted. The calculations based on assumed average hours of sleep per night. In clinical practice, despite recording extensive CPAP use data, it is often difficult to acquire accurate total nightly hours of sleep in actual CPAP patients. Secondly, we assume that the AHI reverts to baseline as soon as CPAP is removed. CPAP is thought to play a role in reducing edema resulting from snoring-associated vibration and apnea-induced suction of the upper airway. The baseline AHI may be reduced by a fraction in chronic CPAP use. As the effect is minimal,
we considered this point negligible. But we also make the assumption that the “AHloffCPAP” matches the AHI of the diagnostic PSG, and we consider the AHI to be uniform across the night, which raises the controversial question: how effective is a PSG as a gold standard for the diagnosis of OSA? PSG has many limitations. Besides night-to-night variability, the AHI does not have a uniform distribution over the night. The AHI fluctuates because of the cyclic alternating pattern of the sleep stages, body position of the patient, medication and alcohol use, nasal congestion, and external factors influencing sleep efficiency, such as a sleep laboratory vs home recording, etc. This is not only a hurdle for the present study, but a handicap for research and clinical management of OSA in general. Some clinicians argue that other PSG variables could be used as an outcome measure; e.g., desaturation index (DI) as a measure of intermittent hypoxia. The latter is also considered to be less susceptible to nightly variability. One could generalize these formulas to other PSG outcomes such as the apnea index (AI) or DI. Others argue that clinical outcomes may be more appropriate. There are more dimensions to consider in clinical management of OSA than AHI alone, e.g., side-effects, partner acceptance, or cost-effectiveness.

Lastly, we assume that there is a linear dose-response between CPAP use and actual patient outcomes; so the more hours a patient uses CPAP, the greater the therapeutic effect. In chapter 8 we provide evidence that clinical outcome is dependent on compliance to treatment in a dose dependent manner. Nevertheless, we question whether the dose-response curve is indeed linear.

On a more general note, the challenge is, in the case of sleep surgery, to perform larger, higher-level, preferably randomized studies that compare surgical treatments, that consider the variety of treatment effects, whilst recognizing the importance of assessment of obstruction site(s) and predictors of treatment outcomes, despite the logistical difficulties associated with random controlled trials on surgical treatment. Last but not least the role of combination therapy (e.g. surgery or MAD and positional therapy) remains to be further elucidated as well as the long-term effect of surgical treatment modalities.
We hope that this thesis serves as motivation for further debate and discussion.

REFERENCES


Ref type: Conference Proceeding


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