TREATMENT OPTIONS FOR OBSTRUCTIVE SLEEP APNOEA

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ABSTRACT

Due to its prevalence, symptoms such as daytime sleepiness, increased risk of accidents, cardiovascular consequences, and the reduced prognosis, obstructive sleep apnoea (OSA) is highly relevant for individual patients and societies. Weight reduction should be recommended in general for obese OSA patients. Continuous positive airway pressure (CPAP) has proven to normalise respiratory disturbances and clinical findings and improve comorbidities and outcome. Although CPAP is not associated with serious side-effects, a relevant number of patients report discomfort, which may limit treatment adherence. Therefore, there is a huge interest in alternative conservative and surgical treatment options. The highest level of evidence can be described for mandibular advancement devices which can be recommended especially in patients with mild-to-moderate OSA, and in patients who fail to accept CPAP despite sophisticated attempts to optimise device, interface, and education. Hypoglossal nerve stimulation might be an interesting option in individual patients. Tonsillectomy is indicated in both children and adults with occluding tonsil hypertrophy. In addition, maxillomandibular osteotomy has been shown to sufficiently treat OSA in the short and long-term. Other surgical options including hyoid suspension, genioglossus advancement, and multilevel surgery might be used in carefully selected, individual cases if other options have failed.

Keywords: Obstructive sleep apnoea, positive airway pressure, alternative treatment options, continuous positive airway pressure (CPAP), adaptive servo-ventilation, mandibular advancement device (MAD), multilevel surgery, neurostimulation of upper airway muscles, position therapy, maxillomandibular advancement, uvulopalatopharyngoplasty (UPPP).

INTRODUCTION

Diminishment and cessation of respiration during sleep are characteristic features of sleep apnoea.[1] It is of crucial importance for the optimal treatment of affected patients to precisely discriminate the phenotypes of the disease:[2] obstructive sleep apnoea (OSA), central sleep apnoea (CSA), and its subtype Cheyne-Stokes respiration, central sleep apnoea emerging under continuous positive airway pressure (also called complex sleep apnoea) and ataxic respiration - a typical but not unique phenomenon in chronic opioid use - differ in clinical symptoms, predisposition, and consequences, and also in the underlying pathophysiology and the consecutive therapeutic approaches.[3] This paper focuses on the therapy of OSA due to its high individual and socioeconomic relevance. However, the principle of CSA treatment should be mentioned briefly; it is based on the optimisation of the underlying cardiovascular, neurological, or renal disease, or – if possible - on the reduction of opioid intake. If this first step fails, it is followed by the application of CPAP, adaptive servo-ventilation, or, in selected cases, oxygen.[4]

The huge majority of patients with sleep disordered breathing suffer from OSA. They typically present with loud and irregular snoring, witnessed breathing disturbances during sleep, and daytime sleepiness.

This triad allows diagnosing OSA with a high pretest probability.[5-8] Nevertheless, patients may also present with fatigue, depression, irritability, sexual dysfunction, or dyspnoea during the night. OSA impairs daytime performance, attention and cognition, reduces ability to drive, and increases the rate of accidents, both in traffic and at the workplace. Moreover, it is independently correlated with cardiovascular consequences, especially arterial hypertension and stroke, and it reduces survival of severely affected patients.[9-11]

Since its first description in the early 1980s, the application of CPAP has become the treatment of choice.[12] It has been proven to remove symptoms and to normalise the risk of accidents, comorbidities, and mortality.[13] The CPAP therapy is not associated with severe complications. However, it may lead to local side-effects, such as dryness of mouth, throat and nose, or irritations of the skin and mucosa. Therefore, the efficacy of the treatment depends primarily on its acceptance and usage by the patients. Several investigations have addressed the long-term CPAP adherence and found figures between 50–70%.[14,15] However, Weaver et al.[16] demonstrated a huge variability of the adherence. Many studies defined sufficient adherence by a daily use ≥4 hours/day, a threshold which was not met by 29-83% of the patients. Factors influencing adherence include the patients´ awareness of the disease and its relevance, the perception of an improvement in symptoms, but also social factors such as economics and marital status.[17-19] Moreover, although CPAP is not associated with severe complications, patients may suffer from local side-effects such as dryness of eyes, mouth, and throat, or irritations of the skin. Therefore, many patients seek alternative treatment options to positive airway pressure (PAP) therapies.

PATHOPHYSIOLOGY OF THE UPPER AIRWAYS OBSTRUCTION

The upper airways, consisting of velopharynx, oropharynx, and hypopharynx are not stiffened by bony or cartilaginous structures and are disposed to collapse. The degree of the obstruction varies, and determines increasing clinical findings from snoring to flow limitations, to hypopnoea and apnoea. It depends on the relation between the dilating intraluminal pressure, muscle forces on the one hand, and the obstructing pressure of the surrounding soft tissue on the other. The critical closing pressure (P_{crit}) describes the tissue pressure which is associated with closure of the upper airways.[20] Skeletal malformations such as verticalisation of the mandible or brevity of the face, predispose to OSA. Fat deposition, enlarged tonsils, or fluid accumulation may additionally increase the tissue pressure. On the contrary, the upper airway muscles counterbalance the mechanical load so that the destruction of the muscles or impairment of their function also increases the collapsibility.[21] Reduction of the muscle tonus increases the collapsibility due to Bernoulli´s principle. CPAP increases the intraluminal pressure on all levels of the upper airways. This has been described as the pneumatic splint. Treatment alternatives have either to reduce the mechanical load, or to improve the muscle function.

Weight Reduction

Two-thirds of the patients with OSA are overweight or obese. Fat deposition in the surrounding issue narrows the pharyngeal diameter and increases the P_{crit}. A gain of body weight impairs the respiratory disturbances substantially more than a reduction improves sleep-related breathing disturbances (SRBD).[22,23] A reduction of the body weight by 10-15% may reduce respiratory disturbances in obese patients substantially.[24] A review of the available data showed a mean reduction of the body mass index (BMI) by 4.7±2.5 kg/m^2 and of the apnoea-hypopnoea index (AHI) by 21±13/hour under dietary approaches. 62% of the patients showed a partial reduction or normalisation of SRBD.[25] Most studies were retrospective and described non-randomised cohorts. However, Johansson et al.[26] applied very low energy diets (550 kcal) and compared it to standard diets in 63 male, obese, OSA patients. They found a substantial reduction of body fat, neck circumference, waist circumference, BMI, and SRBD. In addition, Kuna et al.[27] studied the efficacy of intensive lifestyle interventions in obese Type 2 diabetes patients with OSA over 4 years. Active intervention led to normalisation of OSA in 20.7%, as compared to 3.6% in the control group.

Eskandari et al.[28] studied the effect of zonisamide, a carbonic anhydrase inhibitor, on weight loss and respiratory disturbances. After 24 weeks, the drug treatment reduced body weight significantly while it increased in the control group (-2.7±3.0 kg versus 2.3±2.0 kg, p<0.001). However, the therapy was associated with adverse effects in 38% of patients, and respiratory disturbances improved only mildly. Winslow et al.[29] performed a randomised, double-

blind, placebo-controlled study on the safety and efficacy of a synthetic sympathomimetic amine (phentermine/topiramate) in obese OSA patients. Active treatment reduced the AHI and the body weight significantly. However, more data are needed to recommend the therapy.

Several bariatric surgeries have been investigated, mostly in cohort studies of highly selected patients.[30] They showed substantial reduction of the BMI (10–24.4 kg/m^2) and the AHI (44±22/hour) and 98% of the patients achieved partial reduction or normalisation of SRBD. Thus, reduction of body weight should generally be recommended for all overweight OSA patients. However, as this approach is time-consuming and often insufficient over the long-term, additional rapidly effective therapies (e.g. CPAP) should be applied immediately. In selected, highly-motivated patients who failed several attempts of dietary weight loss, bariatric surgery may be useful.

Positional Therapy

Body position influences the diameter of the upper airways, the critical closing pressure and the respiratory drive. As a consequence, many patients show an increased AHI in the supine position, as compared to the lateral position. Position-dependent OSA is defined by doubling of SRBD in supine position. A prevalence of 50% has been found in younger patients, lower body weight, and less severe OSA.[31-33] Several attempts have been used to avoid the supine position, such as tennis balls sewed into the back of the pyjamas, vests, pillows, position monitor, vibration devices, and verbal instructions.[33-35] However, the body of evidence is limited due to uncontrolled study designs, low sample sizes, and missing long-term results. A recent meta-analysis of three randomised controlled trials including 71 patients with positional OSA, showed that CPAP was superior to positional therapy in improvement of AHI and oxygen saturation.[36] Therefore, position treatment cannot be recommended for the treatment of OSA in general. If they are used in individual cases, efficacy has to be supervised by polygraphy or polysomnography.[25]

Mandibular Advancement Devices

Mandibular advancement devices (MADs) represent oral appliances, which protrude the mandible, thus reducing the load on the upper airways and collapsibility.[37] They widen the diameter of the upper airways, particularly in the lateral dimension.[38,39] MADs have to be discriminated from tongue-retaining devices (TRDs) which are intended to move the tongue forward by suction. However, the level of evidence for TRD´s is insufficient.[25,40] Almeida et al.[41] and Kurtulmus et al.[42] demonstrated a relaxation of the genioglossus muscle under mandibular advancement, indicating the unloading of the upper airways. MADs have proven to reduce obstructive SRBD by 28-80%, with a mean of 55%, as compared to an improvement of 83% under CPAP.[42] CPAP and MADs do not differ substantially in objective evaluations of daytime sleepiness.[40] Mild but significant reductions of arterial hypertension have been shown with both CPAP and MADs. In addition, despite the limited reduction of SRBD, preliminary data indicate substantial improvements of endothelial reactivity and function under MADs.[43-48]

Younger age, lower BMI, female gender, and position-dependent OSA seem to be associated with better success;[40] the devices are more effective in mild-to-moderate sleep apnoea. Recently, Phillips et al.[49] compared CPAP and MAD in a short-term randomised, controlled trial which included 32% of patients with severe OSA. Although CPAP was superior in terms of respiratory disturbances, the treatment options did not differ in parameters of daytime performance and quality of life. However, it is hardly possible to predict the efficacy of MADs based on clinical parameters in individual patients. There is a huge variety of different designs and types of MADs. The preferred adjustable devices allow the dentist to adapt the mandibular advancement according to efficacy and side-effects, which is impossible with monoblock devices. A titration procedure using an adjustable MAD has been recommended; starting with 50% of maximum mandibular advancement.[40,50] Jaw discomfort, tooth tenderness, and excessive salivation are the most prevalent side-effects. However, the majority of patients prefer and report better compliance with MADs as compared to CPAP, although there are only limited data on objective adherence.[41,51-53]

In conclusion, MADs can be recommended in patients with mild-to-moderate OSA as an alternative to CPAP therapy. Nevertheless, the efficacy has to be proven by objective measures. Despite encouraging findings from recent studies, in patients with more severe OSA (AHI >30/h) MADs should still be used cautiously, and are preferred in

patients who are unable to accept CPAP, despite careful attempts to improve adaptation of device and interface, psychological support, and education of patients and relatives.[5]

Training and Stimulation of Upper Airway Muscles

The dilating muscles of the upper airways counterbalance the narrowing forces. Thus, the activity of the genioglossus muscle - the most important dilator - is increased during wakefulness in persons predisposed to OSA. This compensatory mechanism fails during sleep so that the activity of the dilating upper airway muscles diminishes.[54,55] Therefore, the question arose as to whether the function of the muscles can be improved therapeutically. Stimulation of the genioglossus muscle by surface or intraneural electrodes has been shown to reduce the pharyngeal resistance in animal trials, in healthy persons and patients with OSA.[56-60] Training of the upper airway muscles has been trialed by electrical stimulation,[61] speech training, or playing didgeridoo.[62,63] These approaches showed significant, but mild improvements of snoring or AHI. The findings do not allow for a positive treatment recommendation for OSA yet, but support further developments and research.

Most recently, the direct stimulation of the hypoglossal nerve has been introduced to clinical practice.[64] A neurostimulator device is implanted subcutaneously and connected to two electrodes. One lead senses the inspiratory activity of the thoracic muscles; a second lead stimulates the medial branch of the hypoglossal nerve. Thus, each inspiratory effort induces a stimulation of the nerve and consecutively a protrusion of the tongue. Van de Heyning et al.[65] found in a pilot study that BMI ≤32 kg/m^2 and AHI ≤55/h were predictors of effective treatment. In addition, the therapy was less efficacious in patients with a complete concentric collapse of the upper airways during drug-induced sleep endoscopy. Most recently, Strollo et al.[64] performed a multicentre, prospective cohort study in 126 patients for 1 year. Hypoglossal nerve stimulation reduced the AHI highly significantly from 29.3 to 9.0/hour (by 68% in mean). After the 12 months study period, they randomised patients to maintain or withdraw therapy. While the AHI did not differ between the first 12 months and the randomised phase in the maintenance group, it increased substantially in the withdrawal group. In conclusion, hypoglossal nerve stimulation may be a reasonable and efficient alternative to CPAP in OSA patients. However, open questions include the optimal preselection of the patients, the long-term efficacy and side-effects.

SURGICAL TREATMENT OF OSA

Surgical approaches may enlarge the diameter of the upper airways by reducing pharyngeal tissue or skeletal structures or by stabilising the pharynx and minimising turbulences during inspiration. There are several approaches to each level of the upper airways, such as adenoids or tongue base. These options can be combined in multilevel surgery.

The evaluation of surgical therapy is limited for several reasons:

- High quality studies are lacking (even randomised trials with modified control groups).
- Mixed combination of surgical interventions, especially in multi-level surgery, hinders a solid comparison.
- The Sher criteria are often used as primary outcome parameters. However, they do not focus on normalisation of respiratory disturbances but on reduction by 50% to below 20/hours, which may not be sufficient from a clinical point of view.
- It is difficult but crucially important to precisely define the optimal target level for operations.
- Preselection of surgery candidates - whether by clinical or drug-induced sleep endoscopy - is rather the standard than the exception and may lead to substantial selection bias.

Nose

Nasal obstruction does not seem to contribute relevantly to the pathophysiology of OSA. However, it might increase the severity of the disease and the level of CPAP pressure, and might predispose to local side-effects. Several studies describe limited efficacy of surgical interventions at the nose.[66] Due to limited data, nasal surgery should not be recommended for the isolated treatment of OSA, but may be reasonable in case of clinically relevant limitation of nasal airflow.[67] Nasal surgery has been shown to increase CPAP adherence in small sample sizes.[68] This aspect is under debate.

Tonsillectomy

The hypertrophy of tonsils is one of the major causes of OSA in children and might also relevantly contribute to the disease in adults. The existence of an obvious hypertrophy influences the treatment success of surgery more relevantly than potential overweight or disease severity.[69] A partial reduction of the tonsils, for example, by radiofrequency, is mainly used in pediatric OSA with good clinical effect and less bleeding complications.[70] Data on radiofrequency tonsil reduction in adults are rare; a recommendation for this modification in tonsil procedure is open.

Uvulopalatopharyngoplasty (UPPP)

The method has been described in the 1980s by Fujita et al.[71] and has been the standard surgical procedure over a long period of time. However, UPPP does not address obstructions at the level of the tongue base and the hypopharynx, and fails to sufficiently treat OSA in many patients. Walker-Engstroem et al.[72] compared intraoral advancement devices with UPPP for a 4-year follow-up period; here, the MADs reduced respiratory disturbances more effectively than UPPP. In addition, new reports show a benefit of combined UPPP and MAD as compared to UPPP alone.[73] Radical UPPP can be associated with clinically relevant side-effects such as velopharyngeal insufficiency or nasopharyngeal stenosis.[74-76] Less aggressive resection techniques reduce the morbidity efficiently.[77] Although some studies did not show a difference between UPPP and CPAP on long-term survival[78] UPPP cannot be recommended for the treatment of OSA in general. There are several modifications regarding the use of laser, radiofrequency, or suturing which are charming, due to their minimal invasive approach. However, repeated interventions are needed and the techniques are mainly used in snoring and mild OSAS.[79] Therefore, they cannot be recommended as CPAP alternatives in general.

Maxillomandibular Advancement (MMA)

MMA consists of bilateral split ramus osteotomies of the mandible, osteotomy of the maxilla (Le fort I osteotomy), and advancement of both by 10-15 mm in order to enlarge the retrolingual and retropalatal airway. The procedure has been shown to be as effective as CPAP in the treatment of severe OSA, both in short and long-term trials.[25] However, due to possible complications and discomfort, MMA is preserved to patients with severe OSA, who refuse or cannot sufficiently be treated with CPAP.

Distraction Osteogenesis

Distraction osteogenesis (DO) is mainly used in pediatric craniofacial malformations.[80] It may also be indicated in patients in whom maxillomandibular osteotomy cannot be performed. After division of the mandible and the maxilla, the fragments are slowly distracted. Within 4-10 weeks new bone tissue is generated.[81] Unfortunately, upper airway obstruction might relapse with growth as DO is often performed in children with midfacial growth abnormalities.

Hyoid Suspension and Genioglossus Advancement

Hyoid suspension addresses to stabilise the tongue base - which is the area mostly predisposed to collapse.[82] A transcervically applied wire narrows the distance between the chin and the hyoid bone. Although the procedure is invasive, with potential risk for postoperative airway obstruction due to bleeding or swelling, some authors no longer demand intensive care unit observation.[83] There are actual reports with slight surgical modifications showing promising results in reducing OSA burden.[84] Nevertheless, most data are retrospective chart reviews and have severe methodical issues.[85] As AHI is rarely reduced to physiological levels, and the Sher criteria are met in only half to two-thirds of the patients, isolated hyoid suspension is recommended, in CPAP failure only, as a true second choice. Genioglossus advancement is another approach to enlarge the retrolingual space. The muscles of the floor of the mouth and/or the tongue are narrowed to the chin using osteotomies. An actual systematic review showed an overall success of one-third in isolated tongue suspension and 62% of combined procedure with UPPP.[86]

Multilevel Surgery

It has been shown that the upper airway obstruction is often not limited to one level.[87] Moreover, the site of the obstruction may vary throughout the night. Boudewyns and Van de Heyning[88] recently summarised that OSA rarely results from small restricted abnormalities but is caused by diffuse upper airway narrowing in the huge majority of patients. Based on these considerations, staged procedures on different sites of the pharynx called multilevel surgery have been recommended. The stepwise approach begins with

the reconstruction of the nose, UPPP, genioglossus advancement, and hyoid. These interventions are selected based on clinical, radiographic, and/or endoscopic examinations regarding the localisation of the site of the collapse. If the first procedures fail, maxillomandibular advancement may be added as a second step. Another modification is recommended by the Stanford group: stage one consists of a limited mandibular osteotomy with or without hyoid suspension and UPPP. If it fails, maxillomandibular advancement osteotomy is performed in addition.[89]

However, the value of multilevel surgery is difficult to define based on the available data.[25] Patients have to undergo several surgical interventions with repeated anaesthesia, pain, and inability to work. In mild OSA, multilevel surgery can be performed by radiofrequency therapy of soft palate and tongue base. Stuck et al.[90] found improvements of daytime sleepiness and snoring based on subjective estimations in 80 patients who underwent 2.7 sessions of radiofrequency surgery. However, OSA could only be treated sufficiently in one-third of the patients. Similar results were described by Steward et al.[91] Therefore, multilevel surgery is recommended only in selected cases, as second line therapy, following CPAP.[69]

CONCLUSION

In summary, although CPAP is still the standard therapy of OSA, several approaches have been investigated to find sufficient treatment alternatives. MADs show the highest level of evidence and therefore can be offered to a growing number of patients. However, close supervision of the effects and further research on long-term results are needed. While tonsillectomy and maxillomandibular advancement can be recommended based on the specific morphological indication, other surgical therapies are preserved to selected cases and are performed in specialised centres. Hypoglossal stimulation may offer a new option, focusing on the pathophysiological role of the upper airway nerve.

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