Medical treatment of sleep apnea

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Obstructive sleep apnea is a common disorder. Since 1981 the treatment of choice has shifted from tracheostomy or weight loss to uvulopalatopharyngoplasty and then to continuous positive airway pressure. This review encompasses the most recent literature, focusing mainly on current treatment options and other potential and experimental modes of therapy. We review in detail continuous positive airway pressure therapy, including unwanted effects; compliance and possible ways to improve it; and ways to deal with the difficult patient. We also review dental appliances, electrical stimulation, and potential hormonal and nicotine treatment.

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Nasal continuous positive airway pressure

Until 1981, the treatment of choice for obstructive sleep apnea (OSA) was tracheostomy. However, in that year Sullivan *et al.* [1] described the use of continuous positive airway pressure (CPAP) via the nose to treat sleep apnea. It was shown that when adequate continuous positive airway pressure is used, apnea is eliminated, probably by acting as a pneumatic splint and hence preventing obstruction-related desaturation. It is the most important therapeutic advance in the treatment of OSA in the last decade. CPAP is generally a well-tolerated therapy with a reasonable cost-utility ratio [2] and is now considered to be the treatment of choice.

Effects

The goal of therapy is to prevent and reverse sequelae of untreated OSA. A recently published report reviewed in detail the effect of therapy including nasal CPAP on OSA [3••]. More recent developments include the effects of nasal CPAP on neuropsychiatric, cardiovascular, and metabolic disorders.

Treatment of OSA by nasal CPAP improves cognitive and psychologic function as well as daytime hypersomnia. Engleman *et al.* [4••] reported the first randomized placebo-controlled crossover study examining the effect of nasal CPAP therapy on cognitive function, sleepiness, and mood in 32 patients with OSA. They found that when nasal CPAP was used patients had significantly less daytime sleepiness by both subjective and objective measures, as well as improved cognitive performance and mood as compared with placebo use. Refractory seizures have also been found to respond to treatment to OSA. Of seven patients reported to have OSA and medically refractory epilepsy [5], five were treated with nasal CPAP, and on follow-up, four had a clear reduction in seizure frequency.

There are no published randomized clinical trials evaluating the effect of long-term usage of nasal CPAP on ischemic heart disease, cerebrovascular events, or mortality. However, nasal CPAP therapy was recently reported to reverse heart block (sinus arrest and atrioventricular conduction block) in patients with severe OSA with a mean apnea-hypopnea index of 90 [6]. The episodes of heart block decreased significantly from 1575 to 165 during the second nasal CPAP treatment night. In 70% of patients, the heart block was eradicated on the second treatment night. Of the remaining five patients, two had no more heart block after 4 weeks of nasal CPAP and two had significant improvement, but one exhibited persistent increase in block frequency.

The effect of nasal CPAP on insulin metabolism was recently reported by Brooks *et al.* [7]. After 4 weeks of treatment with nasal CPAP in 10 patients with noninsulin-dependent diabetes mellitus and OSA, the mean insulin responsiveness was reported to increase significantly (after excluding one patient due to infrequent nasal CPAP use), although this increased responsiveness was not accompanied by improvement in metabolic control. The mechanism of this beneficial effect of nasal CPAP therapy is not clear. It is possible, however, that treatment of OSA decreases secretion of insulin antagonists such as catecholamines and therefore reduce insulin resistance.

Unwanted effects

Nasal CPAP is a relatively safe mode of therapy. Rare major complications include pneumocephalus [8], mas-

Abbreviations

CPAP—continuous positive airway pressure; **OSA**—obstructive sleep apnea.

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sive epistaxis [9], and bacterial meningitis [10]. Relatively minor complications are much more common. In a recent report of 193 patients with OSA treated with nasal CPAP, dryness of the upper airway was present in 65%, sneezing and nasal drip in more than 35%, nasal congestion in 25%, local skin irritation in 30%, eye irritation in 20%, aerophagia in 16%, sinusitis in 8%, and nosebleeding in 4% [11•]. Despite this high frequency of minor complications, only nine patients stated nasal CPAP therapy was unacceptable because of severe unwanted effects. There was no relationship between the level of pressure and the prevalence of unwanted effects.

These minor complications should be recognized and treated promptly. Humidification of the nasal CPAP airstream may relieve dryness of the nasal mucosa and oropharynx, although the study of Pepin *et al.* [11•] just discussed showed no significant differences in unwanted effects when humidifiers were used. Eye irritation may be prevented by avoiding mask leak and using a well-fitting mask [11•]. Changing the mask size or brand or using nasal pillows has been demonstrated to reduce local skin irritation [11•,12••]. Patients with nasal congestion and rhinorrhea may respond (particularly if they are atopic) to anti-inflammatory nasal sprays (*eg*, antihistamines or steroids), decongestants, or nasal anticholinergic agents [13].

Patients who still cannot tolerate nasal CPAP because of nasal congestion despite a trial of medical therapy, or those with persistent dry mouth or mouth leak, may benefit from using oronasal continuous CPAP with the mask covering both nose and mouth; this technique was recently reported to be effective in alleviating OSA [14,15]. Further studies are needed to confirm the effectiveness and safety of oronasal CPAP before it becomes used routinely.

Compliance

Compliance remains a significant problem with nasal CPAP therapy. Several earlier studies reported compliance rates that ranged from 64% to 82% [16–18]. However, most of these studies used subjective data and basically depend on patient reports or the use of a questionnaire, which may be inaccurate.

The first objective compliance study was reported in 1988 and recorded the machine run-time via a built-in time counter [19]. The mean duration of nasal CPAP use was reported to be 5.1 hours per night. The rate of acceptance, defined as the percentage of patients using the machine for more than 3 hours per night, was about 91%. However, in a similar study using a more strict definition of compliance, *ie*, use of the nasal CPAP machine throughout the night every night for more than 5 hours per night, Meurice *et al.* [20•] reported that of 44 patients with OSA followed up for a mean of 14 months, only 68% were found to be compliant. This group also reported that compliance was directly related to the severity of the syndrome at presentation and the degree of clinical improvement with treatment. Adverse effects were not found to be a factor in determining long-term compliance [20•].

In another study of 47 patients with OSA followed up for 6 months, 20% discontinued therapy within 3 months for various reasons [21]. In the remaining patients, mean compliance, defined as machine run time as a percent of hours of sleep reported, was found to be 68% of total sleep time. The mean effective pressure time per night, which was estimated as the prescribed mask pressure time (measured by mask pressure transducer recorder) as a percent of machine run time, was 91% (4.3 hours) of the time the machine was on (4.7 hours). Therefore, effective therapy was maintained for only about 62% of the total sleep time. Kribbs *et al.* [22] in a similar study reported that of 35 patients only 16 (46%) were found to be regular users of nasal CPAP, which was defined as at least 4 hours of nasal CPAP administration for more than 70% of the days monitored. The rate of use was significantly higher among educated and professional patients.

In a British study in which nasal CPAP was supplied without charge, the mean machine run time was 4.7 hours per night in 54 patients [23•]; however, 32 of these patients had the mask time recorded and it was found that the effective pressure time was 89% of machine run time. In contrast to Meurice *et al.* [20•], compliance was reported to be significantly lower in patients with side effects, and no correlation was found between compliance and severity of sleep apnea syndrome or response to therapy. More recently, Pepin *et al.* [11•] reported a high acceptance rate in OSA patients. Eighty-eight percent of 193 patients used a nasal CPAP machine every night with a mean machine running time of 6.5 hours per night, an acceptance rate that is substantially higher than that reported in other objective studies, although effective mask pressure time was not recorded (Table 1).

Table 1. Summary of objective findings of nasal continuous positive airway pressure compliance in patients with obstructive sleep apnea

Study	Subjects, *n*	Machine time, *h/night*	Mask time, *h/night(%)*[*]
Krieger and Kurtz [19]	45	5.1	—
Kribbs *et al.* [22]	35	4.9	4.5(91)
Meurice *et al.* [20•]	44	6.0	—
Reeves-Hoche *et al.* [21]	47	4.7	4.3(91)
Engleman *et al.* [23•]	54	4.7	—
Engleman *et al.* [4••]	32[‡]	3.7	3.3(89)
Pepin *et al.* [11•]	193	6.5	—

[*]Percentage of total machine time.
[†]See text for definition of compliance.
[‡]These patients were also part of the 54 cases recruited in the study by Engleman *et al.* [23•].

Concern has been raised regarding compliance following a split-night study protocol; this issue was recently

addressed [24], and preliminary results showed that the mean daily rate of nasal CPAP use, which was chosen as the compliance index, was 6.7 hours in 16 of 20 subjects (80%) followed up for a mean of 285 days. This result is superior to that reported in most of earlier objective studies based on routine two-night protocols.

Although it is difficult to objectively compare these study results because of the differences in the definition of compliance, one must conclude that nasal CPAP compliance is generally unsatisfactory. This conclusion should not be surprising because it is a common problem in other chronic illnesses requiring long-term therapy, such as bronchial asthma and epilepsy, in which the rate of compliance has been reported to be 40% and 39%, respectively [25,26]. There is no clear predictive factor for compliance. Although use of a nasal CPAP every night has been shown to be optimal [27], the minimum number of hours per night that is actually required to ameliorate OSA symptoms is not known. Engleman *et al.* [4••] reported significant improvement in daytime symptoms with the use of nasal CPAP, despite a mean machine run time of only 3.7 hours.

There is little published about the education of patients and the role of follow-up in improving compliance. Extensive education and follow-up may play an important role in the first few weeks of therapy because it has been reported recently that the frequency of nasal CPAP use may be predicted by its use in the first few weeks of prescription [22,23•]. Nasal CPAP run time should also be regularly recorded in all patients for continuous objective assessment of compliance, because subjective evaluation based on patient reports has been shown to be an inaccurate estimate of actual daily use [20•,22]. This monitoring would allow early recognition of the infrequent user.

Because upper airway resistance and hence collapsibility of the upper airway is related to a number of variables, *eg*, body position, nasal congestion, sleep stage, sedatives, and so forth, a self-titrating (automatic) nasal CPAP system that senses changes in airway pressure and flow limitation or snoring sounds and adjusts mask pressure automatically may be superior to the conventional manually adjusted nasal CPAP, where a single pressure is used throughout the night. The efficacy of self-titrating nasal CPAP is under current evaluation, and preliminary reports suggest that it is equally effective compared with manually adjusted nasal CPAP therapy in alleviating OSA [28]. In one ongoing study of self-titrating nasal CPAP, the apnea-hypopnea index decreased to less than 5 in 19 of 20 patients; nine of them required a mean airway pressure that was 46% lower than that determined by the conventional nasal CPAP [29]. Nevertheless, because of mouth leaks, the pressure was overestimated in six patients. Although automatic nasal CPAP seems to be as effective as conventional nasal CPAP in some patients, whether its use will improve compliance is not yet known.

Bilevel positive airway pressure

During nasal CPAP therapy, increased work of breathing is required for complete expiration against a high positive expiratory pressure. This requirement may result in a sensation of dyspnea or discomfort and theoretically may decrease the acceptance rate. In such patients, a two-level positive airway pressure device with decreased expiratory pressure has been recommended. Reeves-Hoche *et al.* [30•] recently compared bilevel positive airway pressure versus nasal CPAP compliance and found that the mean nightly time of use over a 12-month period was not different between techniques (bilevel therapy, 4.9 hours; nasal CPAP, 5.0 hours), nor was the effective mask time different (82% and 80% of the machine running time, respectively), suggesting no difference in compliance. Therefore, the use of bilevel positive airway pressure to improve patient acceptance remains a hypothesis that is yet to be proven.

Nasal intermittent positive pressure ventilation

A small group of patients with severe OSA and hypercapnia fail to respond to high nasal CPAP pressures even with the addition of oxygen. In the past, these patients were often treated invasively either by endotracheal intubation or tracheostomy. Recently, Piper and Sullivan [31•] reported the effect of short-term use of nocturnal nasal intermittent positive-pressure ventilation in 13 such patients with severe OSA, obesity (body mass index > 35), hypoventilation and hypercapnia during sleep, and abnormal daytime arterial blood gases (mean $Paco_2$ was 62 mm Hg; in 10 of 13 patients, Pao_2 < 60 mm Hg). They found that 7 to 18 days of nocturnal nasal intermittent positive-pressure ventilation improved daytime arterial blood gases, with mean Pao_2 increasing from 50 to 66 mm Hg and $Paco_2$ decreasing from 62 to 46 mm Hg. Nine patients were capable of starting nasal CPAP again. Three patients required 3 months of ventilation before being switched successfully to nasal CPAP, and only one patient required long-term use of nasal intermittent positive pressure ventilation. The authors concluded that a trial of nasal intermittent positive pressure ventilation should be considered in patients with severe OSA and hypercapnia who fail to respond to nasal CPAP.

The effects of weight loss

In a recent study of morbidly obese patients with severe OSA, the apnea index decreased remarkably from a mean of 40 to 11 after weight reduction surgery [32•]. On long-term follow-up, however, despite minimal change in body mass index, the apnea index increased significantly, suggesting that weight loss alone

does not necessarily cure sleep apnea and its efficacy in ameliorating the disorder may be temporary. In the predisposed individual, aging in addition to obesity may constitute a risk factor for OSA.

Intraoral appliances

Intraoral appliances may be an effective therapy for snoring and OSA. Currently there are about 40 such devices available. They may be grouped into two types: tongue-retaining and mandibular advancement devices. Most of the recent investigations focus on the latter group.

In 20 patients with OSA treated with a mandibular advancement device, the mean apnea-hypopnea index decreased from 57 to 26 [33]. The apnea-hypopnea index was abolished in four patients, decreased by more than 80% in eight patients, and failed to improve in another four patients. Using cephalometric and diagnostic cast analyses, there was a correlation between dentofacial morphology and response to therapy. Thus, the intraoral appliance tends to be effective in patients with micrognathia and a relatively short soft palate. Factors such as overbite, overjet, maxillary jaw length, and hyoid-mandibular distance were found to have a small but insignificant correlation. These parameters may help to distinguish patients with structural and nonstructural OSA.

In another study using cephalometry and polysomnography, 19 patients treated with a mandibular advancement device had a decrease in apnea-hypopnea index from 35 to 13 [34]. There were no significant changes in the mean posterior airway space size nor was there a correlation between baseline posterior airway space and the degree of improvement, which suggests that the mechanism of action of these devices is more complex than just increasing posterior airway space.

O'Sullivan *et al.* [35] noted that the best predictor for therapeutic response was the initial apnea-hypopnea index; the response rate was 70% when the apnea-hypopnea index was 20 to 60, compared with 22% in patients with an apnea-hypopnea index greater than 60. They also reported a high acceptance rate: 79% of patients continued to use the mandibular device regularly. The main adverse effect was mild jaw discomfort on waking seen in 67% of all patients, but the discomfort lasted less than 3 weeks in 39%. Other problems reported were excessive salivation (19%), dry mouth (21%), bruxism (5%), and gum irritation (7%).

These studies suggest that an intraoral appliance is an effective therapy for OSA and snoring. Nevertheless, a large, well-randomized clinical trial is absolutely essential to determine long-term complication and compliance, efficacy in comparison with nasal CPAP, and predictors for therapeutic response. Until such data become available, these devices should only be considered in some patients who cannot tolerate or refuse nasal CPAP.

Hormonal therapy

A hormonal basis for the pathology of OSA has been suggested because it is more common in men and probably among postmenopausal women. This association raises the hypothesis that in postmenopausal women, hormonal replacement therapy may play a role in the treatment of OSA. Cistulli *et al.* [36] studied the effect of estrogen alone and in combination with progesterone on 10 women with OSA (mean apnea-hypopnea index, 43) for a mean of 50 days. They found that, despite an increase in the mean serum estrogen level from 172 to 322 pmol/L, there was insignificant reduction in apnea-hypopnea index during rapid eye movement sleep. They concluded that short-term hormonal replacement therapy has no effect; however, a higher dose, longer therapy, or both may be effective in ameliorating sleep apnea.

In patients with OSA whose apnea worsens with ethanol ingestion, medroxyprogestrone, which probably increases ventilatory drive, may improve oxygenation but not apnea-hypopnea index or apnea duration. This finding has been shown recently in a randomized double-blind, placebo-controlled, crossover trial [37].

When 19 patients (14 men and five women; mean age, 50 years) with sleep apnea and acromegaly were treated with octreotide, a somatostatin analogue [38], and followed up for 6 months, there was a reduction in apnea-hypopnea index from a mean of 39 to 19, and total apnea time decreased from 28% to 15% of total sleep time. There was improved oxygenation, sleep quality, snoring, as well as subjective daytime sleepiness. No correlation was observed between degree of reduction of growth hormone and the effect on sleep apnea severity. These findings suggest that octreotide may improve sleep apnea by an unclear mechanism; however, nasal CPAP is still often needed to ameliorate apnea in these patients.

Transdermal nicotine

Nicotine, a known chemical stimulant, may be a useful mode of therapy in OSA, possibly by increasing muscle tone of the upper airway thereby keeping the airway patent. Twenty nonsmoking snorers (45% with apnea-hypopnea index >10) participated in a double-blind, crossover, placebo-controlled study, using 15-mg transdermal nicotine patches [39•]. There was no clinically significant effect on breathing events or snoring, even in participants with OSA, but there was significantly disturbed sleep quality, *ie*, decreased total sleep time, sleep efficiency, and rapid eye movement sleep as well

as prolonged initial sleep latency. There was, however, no change in arousal index or nonrapid eye movement sleep. There was a trend for shortening apnea duration and raising oxygen nadir with higher serum nicotine levels. This trend suggests that a high serum nicotine level, which probably acts as a stimulant and therefore lowering arousal threshold, may be effective in aborting apnea episodes. More research is required, however, before any definitive statements about this treatment can be made.

Electrical stimulation

The concept of using electrical stimulation in OSA is based on the hypothesis that increasing the activity of the upper airway dilator muscles would decrease the resistance and enhance the patency of upper airway, thereby reversing obstruction. In 1989, based on previous animal studies, Miki *et al.* [40] reported that electrical stimulation is effective in patients with OSA. Hida *et al.* [41] reported on 13 patients who were treated with submental stimulation. After a control night, patients had polysomnographic studies for five consecutive nights with stimulation, followed by three nights without stimulation. There was about a 50% reduction in apnea index (from a mean of 56 to 30 in the fifth night), total apnea duration, and the number of times per hour oxygen saturation dropped below 85% when compared with corresponding values on the control night. Despite this incomplete response, there was significant improvement in Multiple Sleep Latency Test scores and sleep architecture. These effects persisted for the two following nights without electrical stimulation.

Guilleminault *et al.* [42•] recently studied the effect of submental as well as intraoral electrical stimulation on seven patients with OSA and reported its failure to terminate apnea or prevent its occurrence. The duration of apnea may be reduced due to electroencephalogram arousal induced by the electrical stimulation once it exceeds a threshold, but there was no change in apnea-hypopnea index, degree of oxygen desaturation, or mean duration of apnea when no arousal occurred. In conclusion, the results of using submental or intraoral electrical stimulation to treat OSA are still disappointing at this time.

Conclusions

It is clear from this review that nasal CPAP and its derivatives remain the most definitive treatment for OSA despite unwanted effects. Intraoral devices play a role in some patients. The other alternative treatments are either potentially effective only in subgroups of patients or their efficacy has not yet been established.

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