CLINICAL THERAPEUTICS

Continuous Positive Airway Pressure for Obstructive Sleep Apnea

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This Journal *feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author's clinical recommendations.*

During an evaluation by his internist, a 48-year-old man reports that his wife tells him that he snores loudly. Further questioning reveals that he has been falling asleep whenever sedentary. His physical examination is notable for truncal obesity (body-mass index [the weight in kilograms divided by the square of the height in meters], 32) and hypertension (blood pressure, 150/96 mm Hg). He is referred to a sleep specialist for nocturnal polysomnography (sleep study), which reveals evidence of obstructive sleep apnea, with an obstructive apnea–hypopnea index (defined as the total number of episodes of obstructive apnea and hypopnea per hour of sleep) of 50, a nadir value for arterial oxygen saturation of 65%, and an arterial oxygen saturation below 90% during 19% of sleep time. Treatment with continuous positive airway pressure (CPAP) is recommended.

THE CLINICAL PROBLEM

Obstructive sleep apnea, defined as the presence of at least five obstructive events (apneas and hypopneas) per hour during sleep, is found in 9 to 26% of middle-aged people without specific risk factors for the disorder. The obstructive sleep apnea–hypopnea syndrome, defined as the presence of at least five obstructive events per hour with associated daytime sleepiness, is present in 2 to 4% of the same population.[1,2] The prevalence in men is almost three times that in premenopausal women and twice that in postmenopausal women.[3] Other factors associated with an increased prevalence are obesity,[2] older age, and systemic hypertension. The risk of obstructive sleep apnea among relatives of patients with the disorder is almost twice that among neighborhood controls.[4]

Excessive daytime sleepiness and impairments in the ability to sustain attention to tasks, in working memory, and in quality of life are consistently demonstrated in obstructive sleep apnea.[5-7] This condition is also associated with an increased risk of motor vehicle accidents,[8,9] and such accidents (involving people with obstructive sleep apnea) may cost the United States 1400 lives annually.[10]

Cross-sectional data indicate that obstructive sleep apnea is associated with an increased prevalence of cardiovascular and cerebrovascular disease,[11] as well as insulin resistance.[12] A recent prospective cohort study showed that untreated male patients with severe obstructive sleep apnea have significantly greater risks of fatal and nonfatal cardiovascular events (odds ratio, 2.87 and 3.17, respectively) than healthy controls.[13] Untreated obstructive sleep apnea adds an estimated $3.4 billion annually to U.S. health care costs.[14]

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PATHOPHYSIOLOGY AND EFFECT OF THERAPY

Although the primary cause of obstructive sleep apnea remains uncertain, the principal pathophysiological characteristic of the disorder is collapse of the upper airway during sleep.[15-17] Abnormalities of airway structure, such as enlarged tonsils and uvula, and abnormal airway function (primarily a reduction in the activity of the dilator muscles of the pharynx) may contribute to the problem in varying degrees. Progressive upper-airway closure during the transition to sleep is accompanied by complete obstruction of airflow (apnea) or partial obstruction (hypopnea). Hypercapnia and acidosis resulting from hypoventilation stimulate arousal centers in the central nervous system, leading to increased respiratory and pharyngeal-muscle activity. These changes in neurologic function, further stimulated by increasing ventilatory effort itself,[18] ultimately overcome the obstruction, and ventilation resumes. The patient then returns to sleep, the pharyngeal musculature relaxes, and the cycle repeats itself.

With each obstructive event, hypoxemia, hypercapnia, and the generation of negative intrathoracic pressure against the occluded airway characteristically occur, with associated increased right and left ventricular afterload, decreased left ventricular compliance, increased pulmonary-artery pressures, and increased myocardial oxygen demand. Arousal at the termination of the obstructive event is associated with sleep fragmentation and sympathetic discharge, leading to peripheral vasoconstriction and an abrupt increase in systolic and diastolic blood pressures and heart rate, even as the cardiac output continues to fall after the reopening of the airway.[19] Associated decreased cerebral blood flow and oxygenation have been documented.[20,21] The repetitively changing autonomic milieu may be associated with supraventricular and ventricular ectopy and with sinoatrial and atrioventricular block.

CPAP maintains a generally constant pressure in the upper airway throughout the respiratory cycle; an air-pressure source (a special fan) generates airflows — typically ranging from 20 to 60 liters per minute[22,23] — that are delivered into the upper airway through a nasal or oronasal interface. CPAP acts physiologically as a pneumatic splint, inducing patency of the upper airway during inspiration and expiration.[24-26] The resultant reductions in gas-exchange perturbations, respiratory effort,[18] blood-pressure surges,[27] and abrupt arousals[28] all probably play a role in diminishing the propagation of additional obstructive events[15] (Fig. 1).

CLINICAL EVIDENCE

Randomized, controlled trials have shown that CPAP treatment can reduce the cognitive impairment and sleepiness (as gauged by objective and subjective measures) associated with obstructive sleep apnea, with the greatest benefit found in patients with the most severe disorders (apnea–hypopnea index ≥30).[29-32] Sleep quality also improves.[33] In some randomized trials, but not in others, CPAP has also reduced blood pressure in both hypertensive and normotensive patients with obstructive sleep apnea.[34-38]

No data are available from prospective, randomized, controlled trials assessing the effect of CPAP on mortality among patients with obstructive sleep apnea. A recent historical cohort study[39] showed that patients with predominantly severe obstructive sleep apnea (mean [±SD] apnea–hypopnea index, 55±29) who were poorly compliant with prescribed CPAP (using it for less than 1 hour per day) had significantly lower 5-year survival rates than those who were more compliant (using CPAP for more than 6 hours per day [85.5% vs. 96.4%]). These findings are similar to those of another historical cohort study of patients with severe obstructive sleep apnea in which 5-year survival rates were 97% in CPAP-treated patients as compared with 80% in untreated patients, although uvulopalatopharyngoplasty (surgery to remove excess upper-airway tissue) and weight loss were as effective as CPAP.[40]

Randomized trials comparing CPAP with oral appliances, which are designed to reposition the mandible or tongue, have generally shown greater reductions in the apnea–hypopnea index and oxygen desaturation during sleep and greater improvements in sleep efficiency in the CPAP-treated patients. Long-term tolerance of the oral appliances is generally not greater than tolerance for CPAP.[30] No studies have directly compared CPAP with palate surgery (e.g., tonsillectomy or uvulopalatopharyngoplasty). A randomized trial of multilevel,

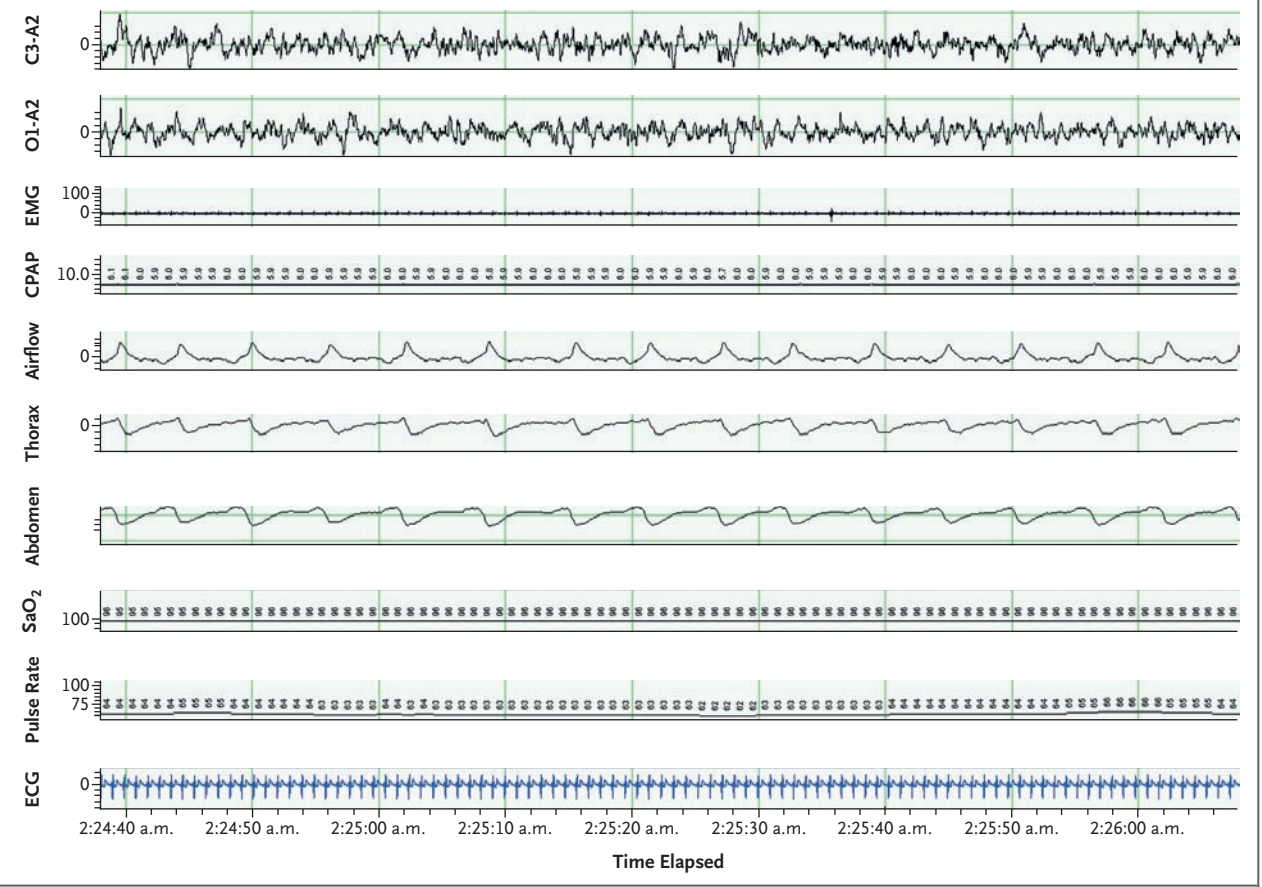


Figure 1. Polysomnogram of a Patient with Severe Obstructive Sleep Apnea, Using CPAP.

This 80-second segment of a nocturnal polysomnogram shows the response of a supine patient with severe obstructive sleep apnea during the application of nasal CPAP at 6 cm of water. The patient is in non–rapid-eye-movement, slow-wave sleep. Respiratory effort has regularized at 10 breaths per minute, airflow is nonoccluded, the heart rate is regularized, and the oxygen saturation of hemoglobin has stabilized at 95% or higher. C3-A2 and O1-A2 denote central and occipital referential electroencephalogram, respectively; EMG denotes submental electromyogram; CPAP continuous positive airway pressure (in centimeters of water); airflow inspiratory airflow in the upper airway; thorax and abdomen thoracic and abdominal respiratory effort, respectively; SaO_2 the oxygen saturation of hemoglobin; pulse rate the continuous oximetry pulse rate (in beats per minute); and ECG precordial electrocardiogram.

temperature-controlled radiofrequency tissue ablation as compared with sham tissue ablation and CPAP in patients with mild-to-moderate obstructive sleep apnea showed a significantly greater decrease in the apnea–hypopnea index from the baseline value in the CPAP group.[41]

CLINICAL USE

CPAP is recommended for patients with symptomatic obstructive sleep apnea even if the apnea–hypopnea index is in the mild range (5 to 15),[42] although evidence-based criteria for the efficacy of CPAP is particularly strong for patients with an apnea–hypopnea index above 15.[42,43] Because of its ease of application and proven efficacy, CPAP is considered first-line therapy for severe obstructive sleep apnea and for obstructive sleep apnea with concomitant cardiovascular disorders.[43]

Other therapies, such as oral appliances, sleep positioning, and uvulopalatopharyngoplasty, should be considered when CPAP is unsuccessful. Site-specific surgery, including maxillomandibular advancement, has been shown to be effec-

tive in selected patients with certain anatomical abnormalities.[44] Tracheostomy is reserved for patients with severe obstructive sleep apnea and cardiorespiratory compromise in whom positive airway pressure is neither tolerated nor effective.

There are no absolute contraindications to the use of CPAP. Bullous lung disease and recurrent sinus or ear infections are considered relative contraindications.[22]

The magnitude of the pressure prescribed for CPAP therapy is generally titrated during polysomnography, often on the same night as the diagnostic study,[42] to find the minimal level of CPAP that is optimal for ameliorating obstructive events, restoring normal levels of arterial oxygen saturation, and decreasing the frequency of arousals in all positions and stages of sleep.[22,43] Ideally, CPAP titration is done after patients have taken their usual evening respiratory suppressants, including alcohol, since the optimal CPAP levels may be affected by such agents.

The optimal delivery system is also ideally established during polysomnography. This includes selection of the best "interface" for the patient. Nasal interfaces (a mask or a pillow system that is fitted around the face, with prongs inserted directly into the nares) are used if possible (Fig. 2).[22,23] A full face mask is used if air leakage from the mouth cannot be controlled. Humidification (cool or heated) may be included to prevent drying of the mucous membranes of the upper airway. Supplemental oxygen may need to be added to the circuit if otherwise optimal pressure levels are not adequate to raise oxygen to acceptable levels during all stages of sleep. Treatment of obstructive sleep apnea with CPAP may result in central apneas, with continued arousals and oxygen desaturation; a comfortable interface that is free of air leaks should resolve this problem without the need to adjust pressures and with acceptable adherence by the patient.[45]

CPAP with delivery of a fixed airway pressure is effective in most patients, but other modes of pressure delivery can be considered. These include bilevel positive airway pressure, auto-adjusted CPAP, and pressure-relief CPAP, all of which entail modification of the exact timing of the pressure delivered, which is intended to improve the patient's comfort and compliance.[24,46,47] However, there is no convincing body of data that any of these modified forms of pressure delivery are better than fixed-pressure CPAP with regard to compliance or efficacy.[47-49]

Figure 2. Patient Receiving CPAP Treatment with Nasal Interface.

An animation of a patient receiving treatment with CPAP is available with the full text of this article at www.nejm.org.

A follow-up visit should generally be scheduled within one month after the initiation of treatment with CPAP, and the daily duration of CPAP use at the set pressures should be monitored objectively.[22,42,43] Such objective monitoring is available with most CPAP units. Patients' reports of use generally overestimate objective measurements by at least 1 hour per night.[31] A systematic education program, including written instructions and follow-up telephone calls, is recommended in numerous practice guidelines for improving comfort and compliance.[42,50] Evidence that adjunctive use of sedative–hypnotic medication improves compliance with CPAP treatment is lacking.[51]

Adjustments of the interface and treatment of nasal congestion and rhinitis are often necessary after CPAP has been initiated. For overweight patients, weight loss is an important adjunct to CPAP therapy. Weight should be monitored as therapy progresses, since weight loss can decrease the apnea–hypopnea index and reduce or eliminate the need for CPAP.[52,53] Repeat polysomnography and CPAP adjustment are typically performed only in the case of substantial weight loss or gain, continued symptoms of obstructive sleep apnea (particularly daytime sleepiness), a major change in cardiorespiratory status, or for the assessment of the efficacy of alternative treatments, such as oral appliances or surgery.[43] The current literature does not contain specific guidelines for objective measurement of improvement in daytime sleepiness with multiple sleep latency testing once treatment with CPAP has begun.[54]

However, such testing should be considered if subjective sleepiness is not resolved despite objective evidence of good compliance with CPAP.

The annual cost of CPAP therapy, based on the 2004 U.S. Medicare fee schedule, includes approximately $1,500 for rental of the device; $200 for purchase of the mask, tubing, and headgear; and $300 for physician office visits.[55] These figures do not include the cost of polysomnography, which is approximately $700 to $900 per study based on current Medicare outpatient rates.[56]

CPAP therapy is usually discontinued by the patient rather than by the physician, and there is little evidence that it can be discontinued without recurrence of obstructive sleep apnea unless substantial weight loss is achieved. One study showed that a single night without CPAP therapy was associated with a return to pretreatment levels of daytime sleepiness and impaired vigilance, although there was a small but significant decrease in the apnea–hypopnea index from pretreatment levels.[31]

ADVERSE EFFECTS

Commonly reported adverse effects of CPAP include irritation, pain, rash, or skin breakdown at mask contact points, particularly the bridge of the nose, or within the nares when nasal pillows are used. Dryness or irritation of the nasal and pharyngeal membranes, nasal congestion and rhinorrhea, and eye irritation from air leakage are also common.[57] Claustrophobia,[58] gastric and bowel distention, and recurrent ear and sinus infections are less common adverse effects. Proper adjustment and fitting of the interface, humidification, and careful adjustment of pressure levels are usually sufficient to allow continued use of CPAP.

Some patients note discomfort with the prescribed level of pressure before they fall sleep, finding exhaling to be particularly difficult.[23] A "ramp" function, which allows the pressure to increase gradually to the prescribed level over a set time (typically 20 minutes) as the patient falls asleep, may improve comfort and compliance. However, this feature also has the potential to reduce adherence as well as to leave the patient with insufficiently treated obstructive sleep apnea.[59]

Pneumothorax, a theoretical concern with positive-pressure ventilation, has not been documented in adults treated for obstructive sleep apnea. Rare instances of cerebrospinal fluid leakage, both spontaneous and associated with prior skull-base trauma, have been reported.[60]

AREAS OF UNCERTAINTY

A major remaining area of uncertainty is the long-term benefit of CPAP in patients with mild-to-moderate obstructive sleep apnea as defined by the apnea–hypopnea index, since CPAP in such situations has not been clearly demonstrated to cause significant reductions in 24-hour blood-pressure levels, cardiovascular events, or motor-vehicle accidents.[8,9,13,61] Furthermore, since not all randomized trials have shown that CPAP lowers blood pressure, even in patients with severe obstructive sleep apnea,[36-38] the long-term effect of CPAP on cardiovascular factors in general and on blood pressure in particular need to be clarified.

In patients with specific cardiovascular and cerebrovascular disorders, including stroke, chronic or acutely decompensated heart failure, and refractory hypertension, the efficacy of CPAP in controlling obstructive sleep apnea and the sequelae of these disorders remains to be defined. Under what circumstances and to what degree CPAP treatment will attenuate the long-term risks of cardiovascular and cerebrovascular disorders in patients with obstructive sleep apnea and concurrent metabolic syndrome are also uncertain.[62] Although CPAP has been used safely and effectively in pregnant patients with obstructive sleep apnea,[63] the specific indications for CPAP use and its effects on maternal and fetal health have not been systematically delineated.

Another area of uncertainty is the long-term cardiovascular and cerebrovascular benefits of CPAP as compared with alternative treatments, including oral appliances, palatal surgery, and supplemental oxygen alone, particularly in more severe cases of obstructive sleep apnea. Finally, there is a need for large randomized studies comparing both the different forms of CPAP interfaces and the different forms of CPAP delivery systems (fixed flexible expiratory pressure and automatic adjustment) with respect to compliance, adverse effects, and long-term outcomes.[23]

GUIDELINES

The American Thoracic Society guidelines of 1994[22] address the initiation and use of CPAP to treat obstructive sleep apnea, establishing CPAP as the

treatment of choice, and include recommendations for optimal titration of positive pressure. The guidelines also suggest the importance of initial follow-up within 1 month after the start of treatment, as well as objective monitoring of CPAP compliance — aspects of CPAP use that are affirmed by practice guidelines recently issued by the American Academy of Sleep Medicine[42] and the Canadian Thoracic Society.[64] Treatment is not recommended for mild, asymptomatic obstructive sleep apnea[43,64] or for patients with an apnea–hypopnea index of less than 5.[65] Practice guidelines of the American Academy of Sleep Medicine and those of the Canadian Thoracic Society also recommend the use of heated humidification and systematic educational efforts as means of improving adherence.[42,64] The recently updated practice guidelines of the American Academy of Sleep Medicine suggest the use of CPAP rather than oral appliances for the treatment of severe obstructive sleep apnea whenever possible and call for follow-up polysomnography to assess efficacy if oral appliances are used.[66]

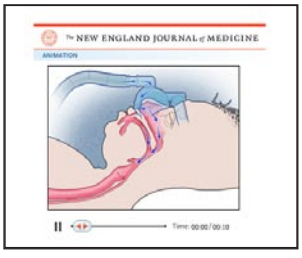
RECOMMENDATIONS

The patient described in the vignette meets the criteria for severe obstructive sleep apnea on the basis of his apnea–hypopnea index and oxygen saturation data. If his initial polysomnographic study did not include CPAP testing, the study should be repeated to confirm that the therapy is effective and to determine the optimal level of airway pressure. Provided that CPAP can be administered effectively in the laboratory, it should be considered the treatment of choice.

The patient should then participate in a CPAP educational and fitting session, with instructions regarding proper hygiene of the humidification and tubing system. It is also important to give the patient a detailed description of the test results and their implications for cardiovascular and neurocognitive sequelae in his situation, as well as what may be expected from consistent use of CPAP, before he begins the therapy. Including his wife, and other family members if appropriate, in the educational session may help ensure compliance with the prescribed treatment and thus its success. Weight-loss counseling should be considered an important part of treatment. The patient should also be counseled regarding the risk of driving before CPAP treatment results in a documented reduction in his excessive sleepiness.

Once the patient has completed education and counseling, CPAP at the appropriately titrated pressure should be prescribed for whenever he sleeps. The patient should return for a follow-up appointment at 30 days, and he should be instructed to call the sleep center if he has problems before that time. The referring physician should receive the report of his evaluation and the recommendations for therapy.

No potential conflict of interest relevant to this article was reported.



An animation showing a patient receiving treatment with continuous positive airway pressure is available with the full text of this article at www.nejm.org.

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