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Positive Airway Pressure Treatment for Obstructive Sleep Apnea*

Rahul K. Kakkar, MD, FCCP; and Richard B. Berry, MD, FCCP

Positive airway pressure (PAP) is the treatment of choice for patients with moderate-to-severe obstructive sleep apnea (OSA). Randomized controlled trials have demonstrated that PAP can effectively reduce the apnea-hypopnea index and improve subjective and objective sleepiness. Some studies have also demonstrated benefits in sleep quality and quality of life for both the patient and bed partner. Observational studies have shown a reduction in the risk of cardiovascular events in OSA patients treated with PAP compared to untreated patients. Since continuous PAP (CPAP) treatment of OSA was described, additional modes of pressure delivery have been developed (bilevel PAP, autoadjusting PAP, flexible PAP). While none of the variants of PAP improves adherence in unselected patients compared to CPAP, individual patients may respond to a change in pressure mode. Attended PAP titration remains the standard of practice for selecting a treatment pressure. However, use of autotitrating PAP devices in the unattended setting can provide an effective titration alternative with careful patient selection and review of titration results. More choices of mask interface are now available to improve comfort and intervene for mask or mouth leaks. However, despite the increase in PAP treatment options, lack of acceptance and inadequate adherence to PAP therapy remain the major causes of treatment failure. Some studies suggest that heated humidification can improve PAP adherence, especially in patients with nasal congestion or dryness. A systematic approach to PAP treatment including education, objective adherence monitoring, early intervention for side effects, and telephone and clinic support is essential to optimize adherence. (CHEST 2007; 132:1057–1072)

Key words: autoadjusting positive airway pressure; continuous positive airway pressure adherence; obstructive sleep apnea; positive airway pressure treatment

Abbreviations: AHI = apnea-hypopnea index; APAP = autoadjusting positive airway pressure; ASV = adaptive servo ventilation; CPAP = continuous positive airway pressure; EPAP = expiratory positive airway pressure; ESS = Epworth sleepiness scale; FOSQ = functional outcomes of sleep questionnaire; IPAP = inspiratory positive airway pressure; NREM = non-rapid eye movement; OSA = obstructive sleep apnea; PAP = positive airway pressure; REM = rapid eye movement; SF-36 = Short Form Health Survey

Since the original description of continuous positive airway pressure (CPAP) treatment by Sullivan and coworkers¹ in 1983, positive airway pressure (PAP) remains the mainstay of treatment for moderate-to-severe obstructive sleep apnea (OSA) in adults.^{2–4} Despite many advances in technology, the major challenge facing clinicians is improving adherence to PAP treatment.⁵ A short review cannot provide in-depth coverage of the large amount of literature that has been published regarding the

efficacy and delivery of positive pressure treatment. The PAP treatment of children, central sleep apnea, or restrictive lung diseases will not be discussed. Our goal is to highlight some important concepts and recent developments that may be relevant to the practicing clinician.

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MECHANISMS OF ACTION AND DETERMINANTS OF PRESSURE

PAP provides a “pneumatic splint” by delivering an intraluminal pressure that is positive with reference to the atmospheric pressure. Upper-airway muscle tone either remains the same or decreases with the application of CPAP.⁶ Imaging studies^{6,7} demonstrate that PAP increases upper-airway cross-sectional area and volume in awake normal subjects and OSA patients with the largest change in the lateral dimensions. A second mechanism by which PAP may affect upper airway size is by increasing lung volume. The increased lung volume provides a downward traction on the trachea (tracheal tug). This action is believed to stretch upper-airway structures and increase upper-airway size. The importance of this second mechanism for the effect of CPAP on the upper airway remains controversial.^{8–9} However, one study¹⁰ found that increases in lung volume induced by applying negative extrathoracic pressure did reduce the amount of CPAP required to prevent airflow limitation in OSA patients during non-rapid eye movement (NREM) sleep.

A number of factors can affect the level of PAP required to keep the upper airway open during sleep. Higher levels of PAP are necessary in the supine (compared to nonsupine) position and during rapid eye movement (REM) compared to NREM sleep.^{11,12} In general, supine REM sleep is the situation requiring the highest pressure. Both elevation of the head of the bed¹³ and weight loss¹⁴ have been shown to decrease the required level of pressure to keep the upper airway open. Weight gain may necessitate an increase in a formerly adequate treatment PAP. Of interest, neither moderate alcohol ingestion^{15,16} nor the benzodiazepine receptor agonist zolpidem¹⁷ impair the efficacy of an otherwise effective pressure level.

PAP MODES AND HUMIDIFICATION

CPAP delivers a predetermined constant pressure during both inspiration and exhalation (Fig 1). Bilevel PAP delivers a separately adjustable lower expiratory positive airway pressure (EPAP) and higher inspiratory positive airway pressure (IPAP).^{18,19} Bilevel PAP may be more tolerable than CPAP for some patients with difficulty exhaling.^{18–21} The IPAP-EPAP differential is useful for augmenting ventilation in patients with concomitant hypoventilation (“overlap syndrome” and obesity hypoventilation syndrome), and most physicians treat patients with these disorders with bilevel PAP.^{20,21} However, many such patients will also improve with CPAP treatment.²²

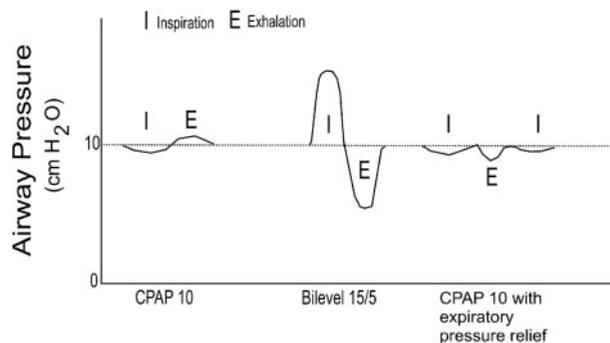


FIGURE 1. Positive pressure modes: CPAP, bilevel PAP, and CPAP with expiratory pressure relief are illustrated.

Autoadjusting PAP (APAP) devices were developed with two potential uses: (1) autotitrating PAP to select an effective level of CPAP without the need for an attended titration; and (2) autoadjusting PAP for long-term treatment with the advantage of delivering the lowest effective pressure in any circumstance.^{23–25} Treatment with APAP would also eliminate the requirement for a CPAP titration. APAP algorithms vary between different devices, but in most instances the pressure changes in response to variations in airflow magnitude, airflow limitation, snoring (vibration), and/or airway impedance.^{23–25} The pressure changes gradually between the preset lower and upper pressure limits to avoid inducing arousal (Fig 2). If none of the monitored variables are detected, the device slowly lowers the pressure to a minimum effective setting. Of note, different brands of devices may respond very differently to changes in airflow.²⁶ Both high airflow leak (mask or mouth), which simulates physiologic events, and the inability to differentiate between central and obstructive apnea by these devices can result in errors in APAP titration.²⁴ The use of APAP devices for autotitration and the effects of long-term APAP treatment on adherence are discussed below. Recently, autobilevel PAP has been introduced (Fig 3). The physician sets the minimum EPAP, maximum IPAP-EPAP difference (minimum is 3 cm H₂O), and the maximum IPAP. The machine then adjusts the EPAP and IPAP to maintain an open airway. The advantages of autobilevel PAP over other PAP modes remains to be demonstrated. However, this mode could potentially be useful in those pressure-intolerant patients who find bilevel PAP alone unacceptable or in patients for whom an effective bilevel pressure is not known.

Expiratory pressure relief (flexible CPAP)²⁷ is a recent variant of PAP that was developed to improve patient comfort by allowing the airway pressure to fall below the prescribed PAP in early expiration (Fig

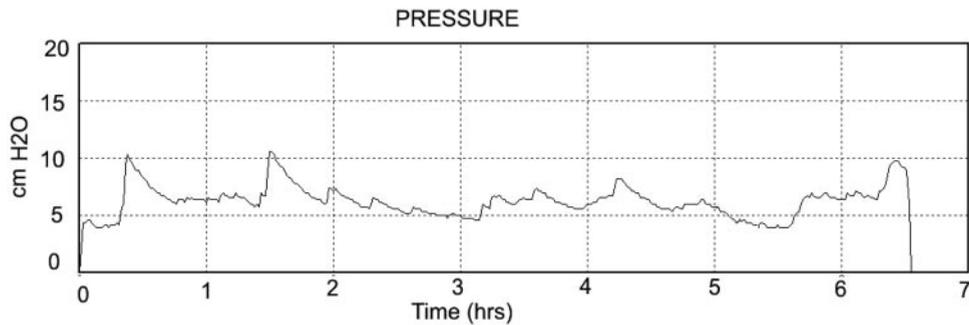


FIGURE 2. An example of pressure vs time for APAP treatment over a night. The device titrated between upper and lower pressure limits set by the clinician. The average pressure is lower than an optimal fixed pressure. In this case, treatment with a fixed pressure would require a CPAP of 10 to 11 cm H₂O.

1) with a return to the prescribed level at end-exhalation. There are two currently available forms of expiratory pressure relief: C-flex (Respironics; Murrysville, PA) and EPR (ResMed Corporation; Poway, CA). With the C-flex device, the pressure drop is progressively greater on settings 1, 2, and 3, but the amount of drop is determined by a proprietary algorithm based on expiratory flow. With the EPR device, settings of 1, 2, or 3 correspond to pressure drops of 1, 2, or 3 cm H₂O, respectively. Flexible PAP is also available with one brand of APAP, bilevel PAP, and autobilevel PAP devices (Respironics). Of note in flexible bilevel PAP the pressure falls at the end of inspiration and the beginning of expiration.

Adaptive servoventilation (ASV)²⁸ is the most recent variant of PAP. ASV was developed to treat Cheyne-Stokes central apnea in patients with congestive heart failure. However, ASV and bilevel PAP devices with a backup rate are also approved for use with patients with complex sleep apnea (central apnea that persists or appears during a PAP titration). In ASV, a level of EPAP is chosen to keep the

upper airway open and the IPAP-EPAP difference adapts between minimum and maximal levels to stabilize ventilation with a goal of providing 90% of the recent average ventilation. With low tidal volume, the IPAP-EPAP increases; with high tidal volume, the IPAP-EPAP difference decreases. A backup rate triggers an IPAP/EPAP cycle if central apnea is present. ASV is not indicated in patients with hypoventilation and may not be as effective in OSA patients requiring a very high level of EPAP.

Today, most PAP devices come with the option of an integrated heated humidification system. Heated humidity can deliver a greater level of moisture than cool humidification and may be especially useful in patients with mouth leak or nasal congestion. Mouth leak can cause a dramatic fall in relative humidity²⁹ in the mask. This occurs because a one-way flow of air out the mouth allows moisture to escape from the system. This dries the nasal and oral mucosa, which increases nasal resistance.³⁰ The level of humidity can be adjusted semiquantitatively by the patient. Adequate cleaning of the humidifier chamber and hoses does require extra patient effort. One study³¹

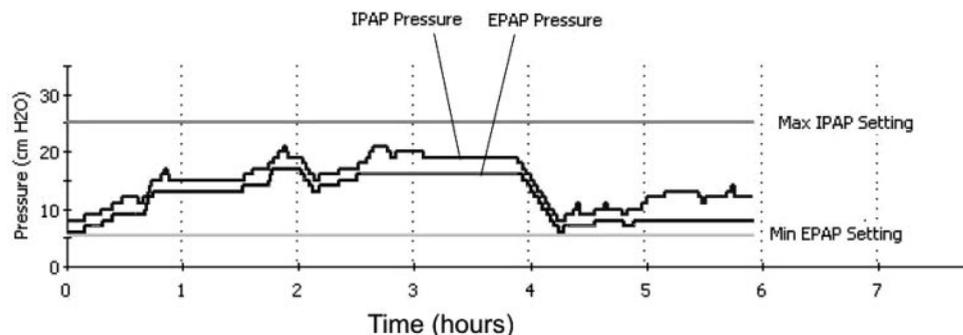


FIGURE 3. A overnight pressure vs time tracing is shown for a patient using autobilevel PAP with a minimum EPAP of 6 cm H₂O and a maximum IPAP of 25 cm H₂O. The 90% IPAP and EPAP pressures were 19.2 cm H₂O and 16.2 cm H₂O, respectively. The average IPAP and EPAP values were 14.6 cm H₂O and 11.8 cm H₂O, respectively.

suggested that use of humidity is associated with an increase in infectious complications.

INTERFACES FOR PAP

For many patients, finding a comfortable interface that does not leak is the major hurdle to adapting to PAP. In our experience, it is not unusual to try several mask types or sizes before finding an appropriate interface. Interfaces include nasal, oronasal (full face),³² or total face masks; nasal prongs or pillows interfaces that fit in the nares³³; or an intraoral device^{34,35} (Oracle; Fisher & Paykel; Auckland, NZ). Masks have air seals made with either a compliant material that bulges out from pressure or a soft gel material. A small orifice(s) in the mask provides an intentional leak to wash out the exhaled CO₂ even at low pressures. Nasal pillows or prongs interfaces may be better tolerated than traditional masks by patients with claustrophobia. Interfaces that fit inside the nostrils (Fig 4) may also provide an effective seal in patients with unusual nasal bridge shapes, those with mustaches, or patients with a lack of support in the area below the nose due to absent dentition. In many patients using a nasal mask, PAP in the nasopharynx moves the soft palate forward against the tongue, thus preventing mouth leak. Other patients must use a chinstrap³⁶ or oronasal mask to prevent mouth leak. Oronasal masks may be better tolerated by patients with substantial nasal

congestion or mouth leak. However, obtaining a good seal with full-face masks is a problem because a large facial area must be sealed. Of note, nasal pillows/prongs interfaces also tend to dilate the external nares and reduce nasal resistance. We have been able to convert some patients with nasal congestion from a full-face mask to a nasal pillows interfaces. A new interface (Hybrid; RespCare; Coconut Creek, FL) is a fusion of nasal pillows and a traditional mask covering the mouth (Fig 4).

INDICATIONS FOR PAP

PAP treatment is considered the treatment of choice in patients with moderate-to-severe OSA usually defined as an apnea-hypopnea index (AHI) $\geq 15/h$.²⁻⁴ The center for Medicare Services will reimburse CPAP treatment for an AHI $\geq 15/h$ in patients with or without symptoms.³⁷ For patients with an AHI ≥ 5 but $< 15/h$, either symptoms (daytime sleepiness, insomnia, impaired cognition, mood disorders) or comorbid conditions (hypertension, a previous cerebrovascular accident, or ischemic heart disease) must be present for reimbursement.

PAP has been shown to reliably decrease the AHI to levels < 5 to $10/h$ in patients with moderate-to-severe OSA.²⁻⁴ Randomized controlled (oral placebo or sham CPAP) studies³⁸⁻⁴⁰ in this patient group have documented improvement in subjective (Ep-



FIGURE 4. Examples of a nasal pillows mask (Swift; ResMed) [left] and a pillows oronasal mask (Hybrid; InnoMed Technologies; Coconut Creek, FL) [right].

worth sleepiness scale [ESS]) and objective sleepiness. The ESS, an index of propensity to fall asleep in eight situations, has been commonly used to measure improvements in subjective sleepiness on CPAP.⁴¹ Objective sleepiness has been tested using the multiple sleep latency test or the ability to stay awake by the maintenance of wakefulness test.

Clinical experience demonstrates that some symptomatic patients with “milder” OSA (often defined as AHI < 15 or 30/h) may also benefit from PAP treatment, although adherence may be lower.⁵ The findings from randomized controlled studies^{42–46} of the benefits of PAP treatment in patients with mild OSA have been inconsistent. Usually an oral placebo was used as the control. Many of the studies included patients with normal or minimally increased ESS scores. Thus, it may not be surprising that while some studies^{42,43} documented a benefit from CPAP, others^{44,45} found no benefit. The Impact of CPAP on Functional Outcomes in Milder Obstructive Sleep Apnea study is a large multicenter study currently in progress with the goal of better defining the effects of CPAP in patients with milder OSA. This National Institutes of Health-funded study uses a parallel-group design to compare the effects of CPAP vs sham CPAP in patients with a respiratory disturbance index from 5 to 30/h.

A limited number of studies have compared PAP to alternative treatments in patients with mild-to-moderate OSA. These have included oral appliances,^{46,47} position therapy,⁴⁸ or upper-airway surgery.⁴⁹ In general, CPAP is more effective at reducing the AHI,^{46,48} but some studies^{48,49} found no greater improvement in subjective sleepiness with CPAP compared to the other treatment studied. Engleman et al⁴⁶ compared an oral appliance with CPAP using a randomized cross-over design in a patient group with a median AHI of 22/h and found CPAP to be superior in reduction of the AHI and ESS score. They did perform a subgroup analysis of patients with mild OSA (AHI, 5 to 15/h) and still found CPAP to be superior, with 14 of 18 patients preferring CPAP. The oral appliance was only adjusted once at the start of treatment. Jokic and coworkers⁴⁸ compared positional therapy and CPAP in a group of patients with mild-to-moderate OSA and positional sleep apnea. While CPAP resulted in a lower AHI and higher minimum arterial oxygen saturation, it did not improve the ESS score, maintenance of wakefulness test latency, or quality of life measures more than positional therapy. Woodson and coworkers⁴⁹ compared CPAP, temperature-controlled radiofrequency tissue ablation, and placebo (probe applications without delivery of energy) using a randomized design in patients with mild-to-moderate OSA. Temperature-controlled radiofrequency

tissue ablation was applied to the palate and tongue in multiple sessions. CPAP and surgery produced similar improvements in the ESS score, but only 9 of 24 patient used CPAP > 4 h per night. In summary, CPAP more reliably reduces the AHI in patients and improves sleepiness as well or better than alternative treatments. Relative patient satisfaction with CPAP vs other treatments likely depends on patient preference.

BENEFITS OF PAP TREATMENT

Multiple effects of PAP treatment have been documented (Table 1). One can classify possible benefits from PAP treatment into four categories: (1) improvement of symptoms such as daytime sleepiness, disturbed sleep, impaired quality of life, or cognition; (2) reduced bed partner sleep disturbance or quality of life; (3) reduction of risk for cardiovascular disease, neurocognitive degeneration, or increased mortality associated with sleep apnea; and (4) reduction in the risk for motor vehicle accidents. As noted above, controlled trials (pill or sham CPAP) have shown improvements in subjective and objective sleepiness after PAP treatment. For example, Jenkinson et al³⁸ using subtherapeutic CPAP as a control demonstrated a decrease in the ESS score and an increase in sleep latency (Osler wakefulness test).

Table 1—Effects of PAP Treatment

| |
|--|
| Higher levels of evidence (multiple randomized controlled trials) |
| Reduction in the AHI (< 10/h) |
| Improvement in subjective sleepiness |
| Improvement in objective sleepiness |
| Lower levels of evidence (uncontrolled studies, smaller number of studies, or conflicting results) |
| Improved quality of life (vitality) |
| Improved nocturnal sleep quality (increased stage 3,4 sleep) |
| Higher level of neurocognitive function (conflicting data) |
| Reduced nocturnal and daytime systemic BP |
| Reduced pulmonary arterial pressure |
| Reduced risk of cardiovascular events |
| Reduced risk of motor vehicle accidents |
| Reduced nocturnal naturessis |
| Reduced diurnal sympathetic activity |
| Reduced inflammatory mediators/coagulation |
| Reduction in overnight hemoconcentration (Kreiger et al ⁷⁷) |
| Decreased morning fibrinogen levels (Chin et al ⁷⁸) |
| Reduced vascular endothelial growth factor (Lavie et al ⁷⁹) |
| Reduced adhesion molecules and reactive oxygen species (Dyugovskaya et al ⁸⁰ and Schulz et al ⁸¹) |
| Reduced platelet activation/aggregation (Bokinsky et al ⁸²) |
| Reduced C-reactive protein and interleukin-6 (Yokoe et al ⁸³) |
| Reduced atrial fibrillation recurrence after cardioversion |
| Improved ejection fraction in patients with congestive heart failure and OSA |

The effect of PAP treatment on quality of life measures has been studied using the Short Form Health Survey (SF-36) and functional outcomes of sleep questionnaire (FOSQ). The SF-36 has been used for many types of health problems, while the FOSQ evaluates the impact of sleepiness on the ability to perform activities of daily living. Some studies showed that PAP treatment improves some SF-36 measures (vitality, energy)^{38,50} and FOSQ productivity and energy measures.³⁹ In contrast, Barbe et al,⁵¹ using a randomized control trial of 6 weeks of CPAP vs sham CPAP treatment in severe OSA (AHI > 30/h) without daytime sleepiness, found no improvement in quality of life measures (FOSQ, SF-36) or cognitive function.

In some severely sleepy OSA patients, there may be a higher-than-normal amount of stage 3,4 and/or stage REM sleep (rebound) on the initial night of CPAP titration. In less sleepy patients, this may not occur possibly due to difficulties adapting to monitoring equipment or the first exposure to PAP. In a randomized controlled trial (placebo capsules vs CPAP), McArdle and Douglas⁵² demonstrated an increase in stage 3,4 sleep and a decrease in stage 1 sleep and arousals after 1 month of CPAP treatment; in this study, the amount of REM sleep did not increase. Another study⁵³ demonstrated a significant decrease in total arousal index with CPAP compared to sham CPAP (2 cm H₂O) after 7 days of treatment. Studies^{54,55} of the effects of PAP on neurophysiologic function have been inconsistent in their findings. There are a number of challenges in performing these studies, including controlling for the effect of learning on repeated testing and the difficulties of completing studies with longer periods of treatment. Bardwell and coworkers⁵⁴ compared 1 week of CPAP vs sham CPAP on changes in 21 neuropsychological tests and found a benefit only when analyzing the entire group of tests. No individual test showed significant results. Henke et al⁵⁵ found that CPAP improved a number of neuropsychological measures but that there was no difference in benefit between effective and ineffective CPAP.

Most physicians treating OSA patients are well aware of the impact of disease and treatment on their patient's bed partner. One study⁵⁶ found CPAP treatment increased the sleep time of bed partners of patients with OSA by almost an additional hour. Another study⁵⁷ found that CPAP treatment improved quality of life measures in the bed partners of patients with sleep apnea.

The third group of PAP benefits includes a possible decrease in mortality from adverse cardiovascular events or other long-term benefits of PAP treatment. Long-term randomized controlled trials of CPAP treatment in patients with OSA are difficult to

perform and for severely affected patients might raise ethical issues. Several observational studies have found a benefit of CPAP treatment in mortality or development of cardiovascular disease. He and coworkers⁵⁸ in a retrospective analysis found an increased mortality in untreated OSA patients with an apnea index > 20 compared to those treated with CPAP. However, no information on the cause of death was provided. Peker et al⁵⁹ observed a group of patients with OSA for 7 years and found a sixfold increased incidence of cardiovascular disease in incompletely treated patients compared to those adequately treated with CPAP. A large observational study by Marin and coworkers⁶⁰ (mean follow-up of 10 years) found about a threefold increase in fatal and nonfatal cardiovascular events in untreated OSA patients, compared to either healthy men or OSA patients treated with CPAP. Another study⁶¹ prospectively followed up a large group of patients over at least 5 years and compared those intolerant to CPAP with those receiving CPAP. Total cardiovascular events were more common in the untreated group (31% vs 18%). The above evidence, although imperfect, suggests PAP treatment reduces the long-term adverse effects of untreated moderate-to-severe OSA. This provides the rationale for the recommendation of PAP treatment for such patients regardless of whether symptoms are present.

CPAP TREATMENT AND CARDIOVASCULAR DISORDERS

A number of studies have assessed the effect of CPAP on systemic hypertension. Becker and coworkers⁶² found that effective treatment of sleep apnea with nasal CPAP for ≥ 9 weeks lowered both nocturnal and daytime systolic and diastolic BP by approximately 10 mm Hg. Strengths of this study included a longer duration of CPAP treatment and use of a noninvasive BP monitoring device that makes continuous measurements and is less likely to cause arousals. It was limited by a relatively large number of dropouts due to technical issues or changes in BP medications. Other investigations have shown smaller^{63,64} or no effects⁶⁵ on daytime BP. These conflicting results may reflect inadequate CPAP treatment (poor adherence), too short a treatment interval, or populations with less severe sleep apnea. In addition, some of the studies included patients who were not hypertensive. Of note, ambulatory BP monitoring can cause arousals from sleep with an associated increase in BP.⁶⁶ Despite the somewhat conflicting data on the effects of CPAP on BP, a standard of practice paper of the American Academy of Sleep Medicine on the use of PAP

treatment⁴ recommended CPAP as an adjunctive treatment for systemic hypertension in patients with sleep apnea.

Patients with OSA also have nocturnal increases in pulmonary arterial pressure secondary to hypoxic vasoconstriction. OSA patients with normal daytime blood gas levels usually have normal or only mildly increased daytime pulmonary arterial pressures.⁶⁷ However, studies^{67,68} have shown that PAP reduces both nocturnal and daytime pulmonary arterial pressure.

Studies have also evaluated the effect of CPAP in patients with OSA and cardiac dysfunction. Kangala and coworkers⁶⁹ found that patients with untreated OSA had a higher rate of recurrence of atrial fibrillation after cardioversion. The increased risk of recurrence was eliminated by CPAP treatment. Other studies^{70,71} have found that CPAP treatment is beneficial in OSA patients with left ventricular failure (improved ejection fraction and symptoms). Another study⁷² found that CPAP treatment reduced the frequency of ventricular premature beats in patients with OSA, heart failure, and a ventricular premature beat rate > 10/h. Studies^{73,74} have also suggested that PAP treatment may improve bradyarrhythmias (sinus pauses, A-V block) or tachyarrhythmias.

A considerable literature exists about the beneficial effects of CPAP on a number of factors relevant to cardiovascular health, including decreased sympathetic activity, decreased markers of inflammation, and improved endothelial function.^{75–83} Some of these results are summarized in Table 1.

CPAP AND MOTOR VEHICLE ACCIDENTS

Untreated OSA increases the risk of being involved in a motor vehicle accident.^{84–87} Sassini and coworkers⁸⁴ performed a metaanalysis of studies published prior to 2000 and found that untreated OSA was associated with a 2.5-fold increased risk. George⁸⁵ examined the incidence of motor vehicle accidents in a group of 210 patients before and after treatment with nasal CPAP. A group of randomly selected drivers served as the control group. Untreated OSA patients had an accident rate three times that of the control group but after nasal CPAP treatment the rate was similar to the control group. Findley and coworkers⁸⁶ studied 50 consecutive OSA patients and used traffic records to verify the incidence of automobile accidents. They also found that nasal CPAP treatment reduced the accident rate.

PAP treatment can result in a reduction in daytime PCO₂ in some patients with OSA and chronic hypercapnia (obesity-hypoventilation syndrome, overlap syndrome).^{22,87} PAP was also effective treatment in OSA patients presenting with decompensated hypercapnic respiratory failure and avoided the need for endotracheal intubation.⁸⁸

Sexual dysfunction is an important problem for patients with OSA and could be related to comorbid diseases such as diabetes. However, an uncontrolled study⁸⁹ found that CPAP treatment of a group of OSA patients with erectile dysfunction resulted in improved erectile function in 75% of the group. Nocturia is a common complaint in patients with sleep apnea that can improve with CPAP treatment. Patients with OSA appear to have increased nocturnal naturesis that is improved with CPAP treatment.⁹⁰ The effect of OSA on insulin sensitivity and leptin is a topic of great recent interest. It has been difficult to determine if OSA has effects independent of obesity. One study⁹¹ found that 1 night of CPAP reduced the nocturnal rise in leptin in patients with OSA, while another study⁹² found no reduction in fasting leptin or hemoglobin A1c in a group of patients with type 2 diabetes after 3 months of CPAP treatment. In contrast, the insulin sensitivity did improve after 3 months of therapy. Another study⁹³ found a larger effect of CPAP treatment on insulin sensitivity in thin vs obese patients. Babu et al⁹⁴ found a very small but significant decrease in hemoglobin A1c after a mean of 83 days of CPAP in those patients with values > 7%. Controlled studies are needed to validate these findings.

POSITIVE PRESSURE TITRATION

Attended polysomnography, which allows sleep stage, arousal, and body position determination, is

Table 2—Problems During CPAP Titration and Typical Solutions

| Problems | Solutions |
|----------------------|--|
| Claustrophobia | Desensitization; nasal pillows; nasal prong interface |
| Mask leak | Careful mask fitting before study; adjust straps; change mask size or type |
| Nasal congestion | Full-face mask; heated humidity; decongestant |
| Pressure intolerance | Avoid rapid increase in pressure; temporary reduction in pressure to allow return to sleep; bilevel PAP; flexible PAP; elevation of head of bed, side sleep position to decrease required pressure |

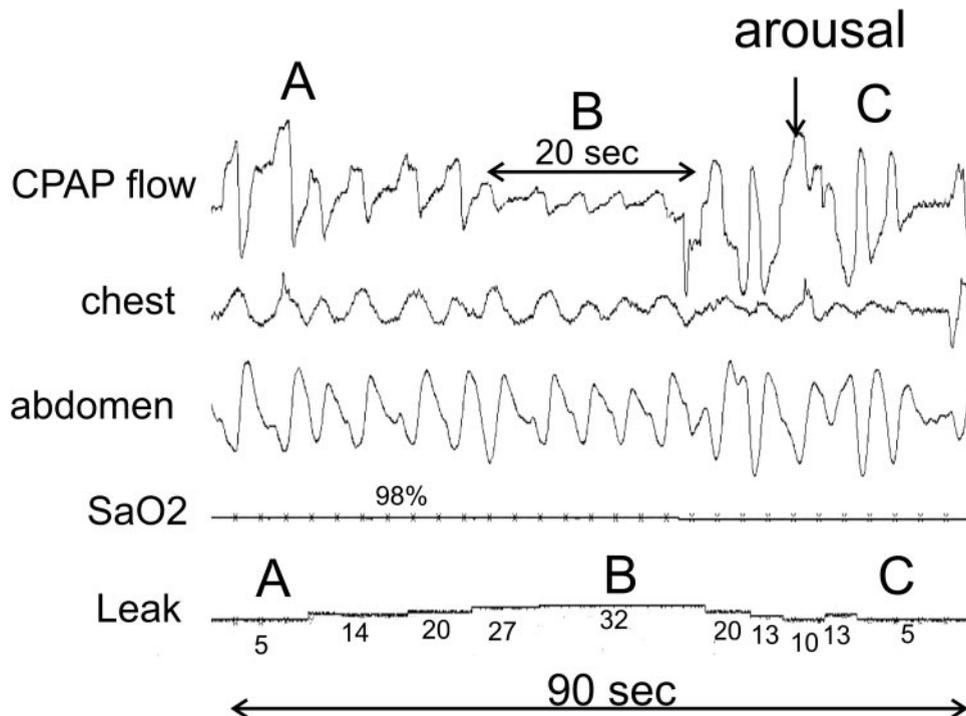


FIGURE 5. A 90-s tracing during a PAP titration. A period of increased leak (B) was associated with a drop in the CPAP flow signal. Note that the flow profile remains rounded in B unlike what is usually seen during obstructive hypopneas. With arousal (C), the leak suddenly dropped. There was minimal body movement from A to C (mask did not move). Video monitoring revealed a mouth opening during B (reprinted with permission from Berry RB, *Sleep Medicine Pearls*, second edition, Philadelphia, PA: Hanley and Belfus, 2003; 130).

the “gold standard” of PAP titration.⁹⁵ The technologist can also address patient complaints, mask or mouth leaks, hypoxemia, or significant arrhythmias. Education about OSA and PAP, mask fitting, and a period of PAP acclimatization should be performed before lights out. Some of the common problems encountered during PAP titration and their solutions are listed in Table 2.

PAP titration requires proper interpretation of information. The flow signal from the analog or digital output of the PAP device derived from an accurate internal flow sensor can be used to detect reductions in flow or flattening (airflow limitation). A flattened airflow profile suggests residual upper airway narrowing.⁹⁶ A leak signal output is also available for recording and helps identify unintentional leak (mask or mouth).⁹⁷ Widely fluctuating leak without a pressure change or body movement suggests presence of an oral leak, which can mimic hypopneic events (Fig 5), prevent airway stabilization, or result in arousal from sleep. The optimal end point of titration has not been scientifically determined. Most laboratories titrate to eliminate obstructive apnea, hypopnea, snoring, oxygen desaturation, and respiratory effort-related arousals. The target AHI is usually < 5 to 10/h, although some centers also try to

eliminate airflow limitation even if not associated with arousal.⁹⁸ As noted above, the highest pressures are usually needed in the supine posture during REM sleep.^{11,12} Therefore an ideal PAP titration is one that demonstrates control of events in the supine position during REM sleep.

One CPAP titration approach is to increase pressure in 2 cm H₂O increments for apnea or 1 cm H₂O for hypopnea/snoring at pressures < 12 cm H₂O and to increase in 1-cm H₂O increments for all types of events when the pressure is > 12 cm H₂O. A starting pressure of at least 4 cm H₂O is required to generate sufficient leak via the antirebreathing aperture to prevent carbon dioxide buildup. Some patients may find it difficult to initiate sleep if the initial pressure is too low. Excessively rapid upward titration does not allow the patient to adjust to positive pressure and leaves the physician who reviews the titration wondering if a lower pressure might have been effective. For bilevel PAP titration, an approach would be to start with 8/4 cm H₂O and then increase both IPAP and EPAP as needed to abolish obstructive events.¹⁸ In general, EPAP is increased to abolish obstructive apneas and the IPAP-EPAP difference increased to abolish hypopneas, snoring, and oxygen desaturation. It is difficult to stabilize the

upper airway of patients with OSA using too low an EPAP or too high an IPAP-EPAP differential. Of note, a different strategy is used for noninvasive ventilation of patients without significant OSA. In this case, a relatively low EPAP (5 to 6 cm H₂O) and high IPAP-EPAP difference (10 to 12 cm H₂O) is often successful.^{3,4}

Complex OSA is a term that has been used to identify OSA patients in whom central apneas persist or develop during PAP titration. *Treatment-emergent central apnea* is another term for central apneas that appear during CPAP titration. This type of central apnea occurs during NREM sleep because the PaCO₂ falls below the apneic threshold. A central apnea may follow an increase in ventilation due to a preceding arousal or an underlying instability in ventilatory control. Central apneas were in fact well described after treatment of OSA with tracheostomy⁹⁹ and tended to resolve with time. Such resolution of central apneas can also occur in some patients with long-term CPAP treatment. Thomas and coworkers¹⁰⁰ described a group of patients with obstructive apnea who displayed a cyclic alternating pattern in the EEG and persistent events during NREM sleep that were not eliminated by increases in pressure. As the pressure level was increased, a "break point" was noted with the emergence of repetitive central apneas. Of interest, these patients did not improve with chronic PAP treatment. The best treatment approach for treatment-emergent central apnea/complex sleep apnea is currently unknown. One can try a reduction in pressure in a patient who previously had fair control of obstructive events (without central apneas) at lower pressures. A slight increase in pressure could be tried if respiratory effort-related arousals are triggering subsequent central apneas. Sometimes, sleep-onset central events will resolve during the study once stable sleep is reached. While technologists often switch from CPAP to bilevel PAP in an effort to abolish central apnea, this can actually worsen the situation unless a backup rate is used. There have been preliminary reports of success in patients with complex sleep apnea with ASV.¹⁰¹

PAP AND SUPPLEMENTAL OXYGEN

Some patients will exhibit significant arterial oxygen desaturation with PAP treatment despite apparently adequate airflow,¹⁰² especially during REM sleep. Persistent hypoxemia on PAP in these conditions may be due to hypoventilation or ventilation-perfusion mismatch (often due to chronic lung disease). Under such circumstances, PAP can be increased to eliminate unrecognized high upper

airway resistance, or CPAP can be changed to bilevel PAP to augment ventilation (higher tidal volume). If these measures are not effective at increasing the oxygen saturation or if higher pressure is not tolerated, supplemental oxygen can be added to PAP.

It is important to recognize that the effective oxygen concentration administered to a patient using PAP will depend both on the supplemental oxygen flow and the machine flow.¹⁰³ Increases in machine flow associated with higher pressures or mask/mouth leak can dilute a given flow of supplemental oxygen. As an example, consider a patient with chronic lung disease and OSA who requires supplemental oxygen at 2 L/min to maintain an arterial oxygen saturation of 94% while awake. With CPAP treatment of 12 cm H₂O, the required supplemental oxygen flow will likely be higher (3 to 4 L/min) depending on the total flow delivered. This assumes that the required fractional concentration of oxygen is the same or higher than the concentration required during wakefulness without CPAP.

SPLIT-NIGHT (PARTIAL) PAP TITRATION

Split-night polysomnography was introduced^{104–107} to obtain a diagnosis and determine an effective PAP on a single night. Underestimation of the severity of sleep apnea (no or minimal REM sleep in the first half of the night) and inadequate time for PAP titration are potential disadvantages of this approach. In a retrospective review of 412 consecutive patients with an apnea index > 20/h, Iber and coworkers¹⁰⁵ found that 78% of the PAP titrations were adequate (the lower of AHI < 20/h or 50% reduction during supine REM sleep). Yamashiro et al¹⁰⁶ found that patients with an AHI > 40/h had similar optimal pressures on a split-night and subsequent full-night CPAP titration. In patients with milder disease a higher average pressure was documented during a full-night PAP titration. The following have been suggested as criteria for a split-night study: a minimum of 2 h of diagnostic monitoring, AHI > 40/h or 20 to 40/h with severe desaturation or other indications for an immediate titration, and 3 h remaining for the PAP titration.^{4,95} Medicare guidelines in some locales require at least 2 h of sleep during the diagnostic portion.³⁷ The effects of split-night vs full-night PAP titration on adherence have not been studied by a prospective randomized trial. Using a case-controlled design, McArde et al¹⁰⁷ found no decrease in adherence in patients treated with a split-night study.

ALTERNATIVE METHODS OF PAP TITRATION

The use of APAP devices for autotitration to select a fixed CPAP treatment pressure has been studied in both the attended and unattended settings.²⁴ The information stored in the device can be transferred to a computer for analysis. Information about time at pressure (adherence), pressure vs time information, leak, and residual AHI information is available to determine the quality of the titration. It is common practice to choose the 95th or 90th percentile pressures as the CPAP prescription pressure.²⁴ On the basis of a systematic review²⁴ of APAP evidence published in 2003, the standards of practice committee of the American Academy of Sleep Medicine²⁵ did not endorse routine use of unattended APAP to select a CPAP treatment pressure. A subsequent large multicenter study¹⁰⁸ found that unattended APAP titration resulted in similar outcomes as attended CPAP titration in a carefully selected population with an AHI > 30/h. Of note, 23% of the potential study group were excluded. The quality of APAP titrations was assessed in detail (duration of use, residual AHI values). Unacceptable titrations were repeated, or patients were referred for an attended titration if necessary. Thus, it appears that in carefully selected populations with proper education and careful review of titration results that unattended APAP titration can be successful in many patients. APAP titration is a useful option when access to polysomnography is not possible or delayed, when the results of an attended titration are

inconclusive, or when there is a need to check the efficacy of a given prescription pressure (recent weight gain).

A number of other alternatives to attended PAP titration have been proposed. These include initiating treatment using a pressure prediction equation,¹⁰⁹ with further pressure adjustments made by medical personnel based on bed partner observations¹⁰⁸ or by the patient based on comfort and perceived efficacy (self-titration).¹¹⁰

SIDE EFFECTS OF PAP

There are many side effects associated with PAP treatment^{5,111–114} that if left untreated could lower the acceptance and adherence rates of PAP treatment. Common side effects and possible interventions are listed in Table 3. Involving both the patient and the spouse in the search for solutions to side effects (a team approach) is often helpful. The spouse may recognize mask or mouth leaks when the patient does not. Mask discomfort is often the most common reason for discontinuing CPAP treatment.¹¹¹ Obtaining an adequate mask fit may require trials of several different brands and types of masks. As noted above, there are a wide variety of interfaces that are available. Adequate care of masks and replacement of masks when the sealing membrane deteriorates are also necessary.

Table 3—PAP Side Effects and Possible Interventions

| Side Effects | Interventions |
|---|---|
| Due to mask | |
| Air leaks (conjunctivitis; discomfort; noise) | Proper mask fitting; proper mask application (education); different brand/type of mask |
| Skin breakdown | Avoid over tightening; intervene as above for leaks; alternate between different mask types; nasal prongs/ pillows; tape barrier for skin protection |
| Mouth leaks | Treat nasal congestion if present (see below) |
| Mouth dryness | Chin strap; heated humidity; full-face (oronasal) mask; consider bilevel PAP, flexible PAP, lower pressure, APAP |
| Mask claustrophobia | Nasal pillows/prongs interface; desensitization |
| Unintentional mask removal | Low-pressure alarm; consider increase in pressure |
| Nasal symptoms | |
| Congestion/obstruction | Nasal steroid inhaler; antihistamines (if allergic component); nighttime topical decongestants (oxymetazoline); nasal saline solution; humidification (heated); full-face (oronasal) mask |
| Epistaxis | Nasal saline solution; humidification (heated) |
| Pain | Humidification (heated) |
| Rhinitis/rhinorrhea | Nasal ipratropium bromide |
| Other problems | |
| Pressure intolerance | Ramp; flexible PAP; bilevel PAP; APAP; lower prescription pressure temporarily; accept higher AHI; lower pressure and adjunctive measures (elevated head of bed, side sleeping position, weight loss) |
| Aerophagia/bloating | Bilevel PAP; flexible PAP; reduce pressure |

The PAP treatment of sleep apnea is somewhat unique compared to treatments for other chronic disease.¹¹⁵ First, technology exists to allow the physician to objectively determine the amount and pattern of use (adherence). Second, the outcome difference between low and high adherence is relatively high compared to many other chronic diseases. That is, PAP is very effective but only if used on a regular basis.

Acceptance is usually defined as patient's willingness to undergo a PAP titration and take a PAP device home and use it for at least 1 week.⁵ Adherence (compliance) is defined as the extent to which a person's behavior coincides with the medical or health advice. One commonly used definition of adequate adherence is PAP usage of ≥ 4 h per night for $> 70\%$ of days^{5,116}. This not a completely satisfactory definition because a significant proportion of patients likely require > 4 h per night of use for maximal benefit. A comprehensive review⁵ of CPAP literature published prior to 2003 found nonacceptance rates to vary from 5 to 50%, with average approximately 20%. Another 12 to 15% can be expected to stop PAP treatment within 3 years. Of those using PAP, adherence rates (> 4 h use for 70% of days) have varied from 40 to 80%, with the highest figures reported for studies^{5,116,117} with a systematic program for PAP treatment. These CPAP adherence statistics are comparable to those for oral medication treatment of chronic diseases. A metaanalysis¹¹⁵ of adherence to medical treatment found that at least 40% of patients take prescribed medications incorrectly or not at all.

Determination of objective adherence is essential because many patients overestimate their PAP use.^{118,119} The original method of determining objective adherence used a run-time meter from which one could determine the average time the unit was turned on. Most current devices now determine time at pressure (actual use) and can provide a detailed electronic diary of the amount and pattern of use. The pattern of use can be instructive. For example, one might determine that a patient routinely removes the CPAP mask at 4:30 AM while reporting a 6:30 AM wakeup time. The reason for this pattern of use could be addressed and the patient educated about the severity of early morning arterial oxygen desaturation. Adherence information can be assessed through memory cards, modems, wireless communication, or direct transfer from the blower unit to a computer. Early access to adherence information is essential. Weaver and coworkers¹²⁰ found that the pattern of use by adherent and nonadherent patients differed as early as 4 days of treatment. Patients

adherent over the first 1 to 3 months tend to continue to accept positive pressure treatment.

PAP EQUIPMENT AND ADHERENCE

Improving patient tolerance of PAP is one of the main driving forces for the development of alternative modes of PAP. However, pressure intolerance is not a common complaint among PAP users,⁵ and a comparison between groups of consistent and intermittent CPAP users found no difference in the level of pressure.¹²⁰ A change in PAP mode may dramatically improve adherence in individual patients. Symptoms of bloating, mouth leak, or pressure intolerance may improve with a switch from CPAP to bilevel PAP. However, bilevel PAP has not been proven to improve PAP adherence in unselected patients.¹⁹ In theory, the APAP delivery of the lowest effective pressure might improve PAP acceptance or adherence.²⁴ The mean nightly pressure might be lower than a single higher pressure effective in all circumstances. For example, a pressure of 12 cm H₂O might be needed during supine REM sleep while a pressure of 6 cm H₂O might be effective during lateral NREM sleep. If the patient slept for much of the night in the lateral position, the mean pressure might be considerably lower than the required prescription pressure of 12 cm H₂O. Studies^{24,121} comparing APAP treatment with CPAP with respect to adherence have found conflicting results. A metaanalysis¹²¹ of a number of studies concluded that APAP treatment does not result in higher adherence. This result may not be surprising when one considers that pressure intolerance is not an important side effect for a majority of patients. In addition, the difference between the mean APAP pressure and the optimal CPAP level may only be 1 to 2 cm H₂O. A study by Hukins¹²² also found that APAP did not increase adherence compared to CPAP. However, objective leak was lower and satisfaction higher with APAP. Individual patients with mouth/mask leak problems may find APAP more tolerable. In summary, the higher cost of APAP units and lack of improved adherence eliminates the routine use of APAP for OSA treatment. However, individual patients may find APAP more acceptable than CPAP.

The potential of flexible PAP to improve patient comfort has resulted in widespread use of this PAP variant. However, to date, relatively little data have been published proving an advantage over routine PAP. Aloia et al²⁷ showed that use of a C-flex device provided a statistically significant improvement in

adherence (4.2 ± 2.4 h vs 3.5 ± 2.8 h) [mean \pm SD], but the study design used sequential patient groups rather than a randomized design. Therefore, further studies using randomized prospective designs are needed to confirm this result.

The effect of humidification on PAP adherence has been studied by a number of investigators. Two controlled studies^{123,124} found an improvement in adherence with humidification, while other studies^{3,125} did not find an advantage for routine use of humidity during the initial titration or treatment. One might make a case for reserving humidification for patient groups more likely to benefit (nasal congestion, mouth leak). However, the need for humidification cannot always be predicted.

FACTORS DETERMINING PAP ADHERENCE

In theory, it should be useful to understand the factors predictive of poor adherence to PAP treatment and thus allow targeting of patients at high risk for treatment failure. Predictive factors have not been completely consistent between studies,^{5,113,114,126,127} but in general factors found to increase PAP adherence are increased severity of sleep apnea, greater daytime sleepiness, perceived symptomatic benefit, and a higher AHI. Factors that negatively influence adherence are lack of daytime sleepiness, lack of perceived benefit, side effects from PAP, previous uvulopalatopharyngoplasty, nasal obstruction, and claustrophobia.^{5,114} Of interest, studies have not found pressure level to be predictive of adherence.

A number of social cognitive models have been applied to the treatment of chronic disease including PAP treatment. In one model⁵ of chronic disease, the patient's perception of the relative weight of costs (side effects, inconvenience) vs benefits (symptom improvement) is viewed as determining adherence. Using social cognitive theory,¹²⁸ several components have been hypothesized to be relevant to CPAP adherence: (1) perception of risk from un-

treated sleep apnea, and (2) expectations regarding treatment outcome (outcome expectancies) and confidence or volition to engage in treatment behavior (treatment self-efficacy). This model provides a means of assessing factors predictive of poor adherence and provides a structure for the design of more effective interventions.

IMPROVING PAP ADHERENCE

A number of prospective studies have tried to document improvements in adherence by various interventions. A problem with these studies^{5,129} is that many used a "package" of interventions so that the importance of each individual component cannot be determined. A list of techniques that alone or as part of a systematic approach have been shown to improve adherence are listed in Table 4. Simple interventions using the telephone can increase adherence,¹³⁰ and group education provides a cost-effective intervention.¹³¹ Early and frequent initial follow-up after PAP initiation to troubleshoot problems with PAP usage, and at least yearly follow-up thereafter is recommended. It is possible that multidisciplinary PAP adherence clinics involving respiratory therapists, sleep physicians, otolaryngologists, and sleep psychologists may improve the adherence significantly.

FUTURE CHALLENGES FOR PAP TREATMENT

Better evidence of the long-term benefits of PAP treatment is needed to support our recommendation that PAP should be used even in the absence of significant symptoms when severe sleep apnea is present. Identification of those patients who are most likely to accrue health benefits from PAP and more information on the amount of use required for benefit would be extremely useful. An example of the type of study needed is the Apnea Positive Pressure Long-term Efficacy Study,¹³² a current multicenter study, with the goal of determining the size, time course, and durability of the effects of long-term CPAP treatment on neurocognitive function, mood, sleepiness, and quality of life.

It is also imperative that technologies continue to improve comfort and convenience (device size and noise) of PAP treatment. Additional improvements in PAP interfaces are still needed. Is it realistic to expect that three to six sizes of a mask will work with the large spectrum of facial contours? Change in policies controlling reimbursement for PAP interfaces to make allowance for several mask changes at the initiation of treatment would be very useful. The

Table 4—Methods To Improve PAP Adherence

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|--|
| Education about OSA and PAP by staff, videotape, printed information |
| Involvement of significant other/spouse |
| Extended in-hospital (2–3 nights) stay |
| Subsequent mask and headgear adjustment or change |
| PAP help line |
| Unsolicited telephone follow-up |
| Early interventions for side effects and concerns |
| Objective monitoring of adherence |
| Early and regular clinic visits |

optimal approach to the treatment of sleep apnea may benefit from information gained in treating other chronic diseases. The lack of coordination between sleep centers, physicians, and durable medical equipment providers must be eliminated. Studies documenting the value of integrated PAP delivery systems are needed to convince governmental and insurance carriers to eliminate the financial barriers to implementing this approach.

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