Sleep Medicine

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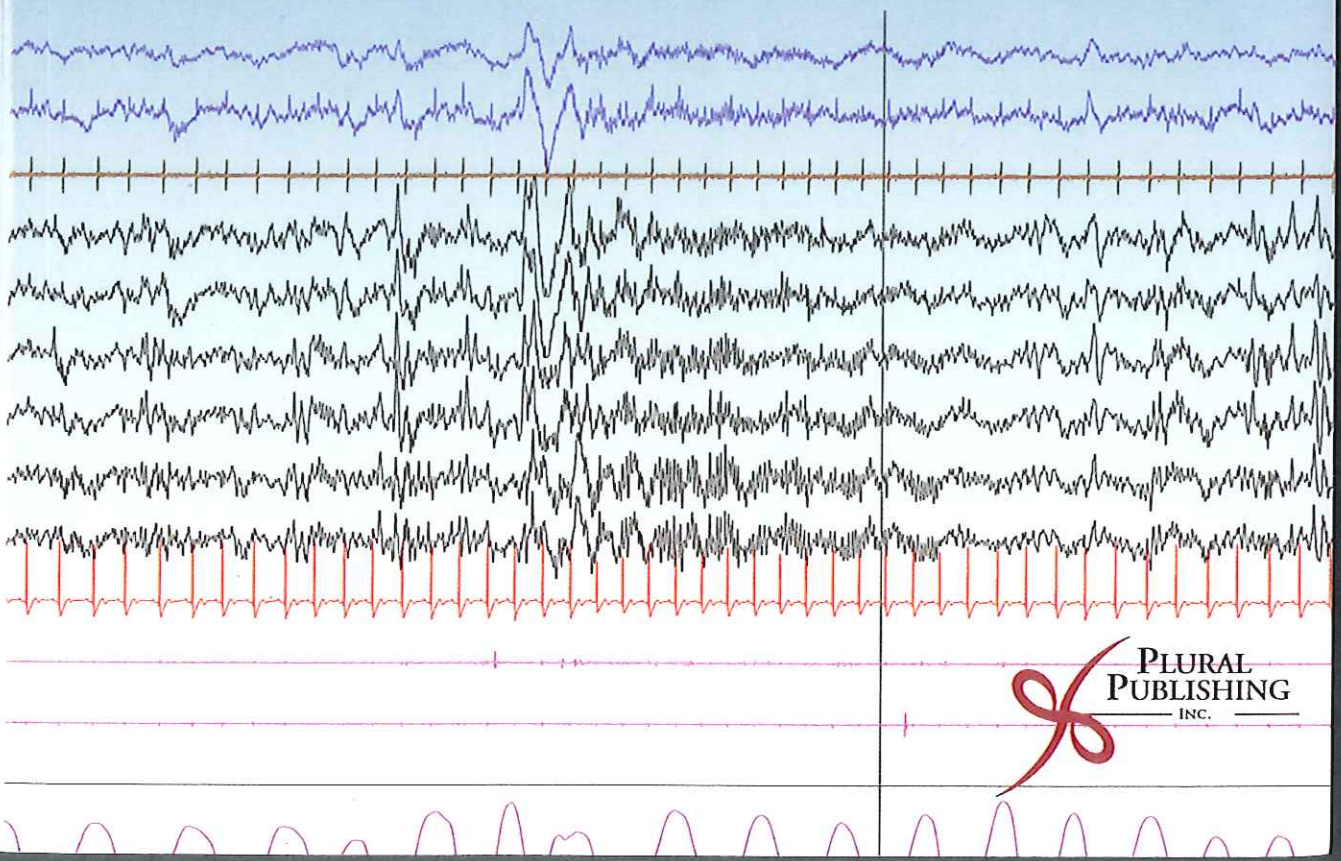

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CHAPTER 17

Position Restriction Therapy and Nasal EPAP in the Treatment of Obstructive Sleep Apnea

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INTRODUCTION

Standard treatments for obstructive sleep apnea (OSA) traditionally have included continuous positive airway pressure (CPAP), oral appliances, upper airway surgery, and behavioral therapy. Although CPAP is viewed as the gold standard of therapy, compliance with CPAP is suboptimal for many patients, accentuating the need for other treatment options. One type of behavioral therapy, position restriction therapy, is described below, along with a newer treatment modality, nasal expiratory positive airway pressure (EPAP).

POSITION RESTRICTION THERAPY

That sleeping posture effects breathing in sleep must have been obvious to annoyed observers long before the rediscovery of sleep apnea. Bed partners learned that an elbow to the ribs of a snorer not only caused immediate cessation of the harsh inspiratory sound, but could result in a more prolonged diminution of snoring if the arousal was accompanied by a shift away from the supine position. We now know that snoring is the audible signature of inspiratory flow limitation. Snoring anchors one end of what Lugarisi called the "Heavy Snorers Disease," the spectrum of disorders characterized by a sleep-related collapse of the upper airway, from "simple" snoring to upper airway resistance syndrome to severe nonpositional OSA. It is now well documented that posture plays a major role in the frequency of abnormal breathing events during sleep. The majority of patients with obstructive sleep apnea have more apneas and hypopneas when supine than when sleeping on their side.

Definition and Prevalence of Positional Sleep Apnea

Cartwright was the first to formally study the effect of sleep position on sleep apnea.[1] She studied 24 male OSA patients and calculated the apnea/hypopnea index (AHI) separately for time while on the back and on the side positions. The number of obstructive events while supine was roughly twice that while on the side. Thirteen of the 24 (54%) met her later definition of positional sleep apnea, which is an AHI supine (AHI-S) that is more than twice the nonsupine AHI (AHI-NS), whereas the remainder had a ratio of AHI-NS to AHI-S of greater than 0.5. Five of the 24 patients had an AHI on their side that was within normal limits. Pevernagie and Shepard did a retrospective analysis of 98 male patients with an overall AHI > 10.[2] After eliminating from analysis those with insufficient sleep time in one or more studied sleep postures and/or sleep states, 81 patients remained with more than 30 minutes of NREM sleep time. Of these, 49 (60%) were positional and 30 (37%) were nonpositional. Two patients who had an AHI-NS that was over twice the AHI-S were deemed to be "reverse positional." There were 33 patients with at least 10 minutes of REM sleep in both postures. During REM sleep, the positional effect on AHI was diminished with 16 (48%) deemed positional, 15 nonpositional, and 2 reverse positional. The authors also noted that in patients with positional sleep apnea the effective CPAP pressure required was less than for those who were nonpositional. Oksenberg and colleagues analyzed the results of laboratory polysomnography in 666 consecutive patients with an overall AHI of > 10.[3] Of these, 574 meet the study criteria for age (> 20 years), body mass index (BMI) over 20, and more than 30 minutes sleep while either supine or nonsupine. Of this study group, 321 (56%) were positional and 253 (44%) were nonpositional.

In both the Cartwright and Oksenberg studies, nonpositional patients were significantly heavier than positional patients. Other smaller studies have also noted a link between nonpositionality and obesity. All three studies noted that patients with positional OSA slept significantly longer and more deeply than those with nonpositional OSA. However, the main predictor of nonpositional OSA was overall AHI. Oksenberg found that 65 to 69% of patients with an overall AHI in the mild to moderate range (10 to 40 events per hour) had positional OSA, but only 32.4% of those with an overall AHI of greater than 40 were positional. The results of all these studies are consistent with everyday clinical experience in which patients with severe OSA are much less likely to be positional.

In the three studies cited, positional OSA was defined as having an AHI-NS/AHI-S of < 0.5, and nonpositional as having a ratio of > 0.5. This continues to be the most widely used definition. However, Marklund et al suggested other criteria for positional dependency of OSA patients.[4] They reported that supine-dependent OSA could be defined by a supine AHI ≥ 10 together with a lateral AHI < 10, and nonsupine-dependent OSA considered in patients with a lateral AHI ≥ 10. Clearly, this later definition makes some sense when position restriction therapy is being considered clinically. If a person has an overall AHI and AHI-S that is abnormal, but an AHI in the nonsupine position that is within normal limits (here defined as an AHI < 10), then preventing that person from sleeping supine would

be undeniably successful treatment. One of the authors (PW) has adopted this definition for clinical reports of positional sleep apnea. When the overall and AHI-NS are greater than 10 but the AHI-NS/AHI-S ratio is less than 0.5 the term "nonpositional but supine position exacerbated OSA" is used.

Mechanism of Action

Gravity and posture can interact to effect breathing during sleep in at least two ways. The most obvious and most frequently cited is the effect of gravity on the soft tissues of the pharynx altering the passive mechanical behavior of the collapsible segment. During sleep, when the muscles responsible for holding open the pharyngeal passageway during inspiration are relatively inactive, the supine posture allows gravity to increase the tendency of the tongue to fall back against the palate, causing further narrowing of an already compromised airway. This same gravitational force can act on the structures other than the genioglossal muscle. In the supine position, sleep induced hypotonia of the masseter and lateral pterygoid muscles allow the opening of the mouth and further dorsal displacement of the mandible and tongue. Penzel et al measured the collapsibility of the passive pharynx in supine and lateral positions in 16 male patients with mostly severe sleep apnea (average AHI 48.9).[5] They found a major effect of body position, with collapsibility decreasing significantly with a change from the supine to the lateral posture. This was true for light and slow-wave NREM sleep and for REM sleep.

One of the most conclusive studies on the effect of gravity on the passive pharyngeal airway was performed by Isono et al.[6] They induced total muscle paralysis with general anesthesia in 8 patients with sleep apnea, thus eliminating neuromuscular factors. They then measured pharyngeal airway size under various imposed static airway pressures in both supine and lateral positions. Cross-sectional area of the pharynx was measured at two sites (retropalatal and retroglossal) using endoscopic images. Static pressure-area curves of the pharynx in both positions were then plotted. As illustrated in Figure 17-1, the passive pharynx was much more collapsible in the supine position than in the nonsupine position.

The effect of posture on pharyngeal protective reflex mechanisms was investigated by Malhotra et al.[7] They measured the electromyogram of the genioglossus and tensor palatini muscles during basal breathing and in response to negative pressure pulses during wakefulness and sleep in 17 normal subjects. Compared to responsiveness during wakefulness, the genioglossal response during sleep was significantly increased in the supine position and decreased in the nonsupine position. However, despite the augmented negative pressure reflex, pharyngeal collapsibility remained greater in the supine than the nonsupine posture.

The second mechanism whereby changing from the supine to the nonsupine position could decrease frequency of obstructive breathing events is due to the effect of gravity on the chest wall. The chest wall can be defined as all nonairway and lung structures that move during breathing, and thus includes the rib cage and the abdomen. The amount of gas remaining in the lungs at the end of a normal expiration (functional residual capacity or FRC) when no respiratory muscle

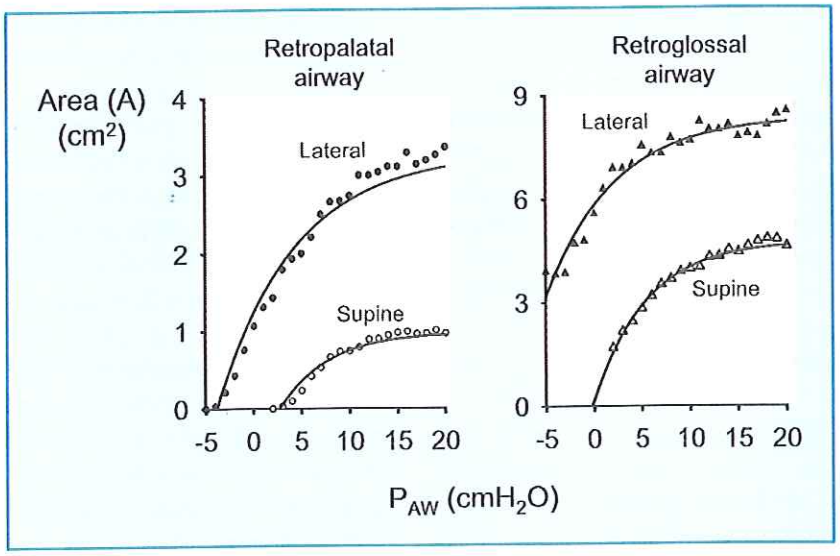


Fig 17–1. Representative static pressure-area relations obtained from one subject, showing difference of the relations at the level of retropalatal and retroglossal airways between the supine and lateral positions. A = cross-sectional area; P_{AW} = airway pressure. Reproduced with permission from Isono S, Tanaka A, Nishino T. Lateral position decreases collapsibility of the passive pharynx in patients with obstructive sleep apnea. *Anesthesiology.* 2002;97:782. Copyright 2002 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

activity is present depends on the balance of forces acting on the chest wall. These forces include the inward recoil of the lungs, the outward recoil of the rib cage and, especially in the supine position, the force on the diaphragm from abdominal contents. The direction of gravitational force and thus FRC depends on posture. FRC is significantly less when recumbent compared to sitting and significantly less supine than in the lateral decubitus position. This increase in FRC in the nonsupine position compared to the supine position can effect breathing during sleep in two ways. First, it is well known that an increase in FRC causes a caudal tug on the upper airway and that this tug tends to decrease airway collapsibility. Second, an increase in FRC increases oxygen stores in the lung, buffering changes in blood gases and thus decreasing plant and loop gain. The net effect is a stabilization of respiratory control.

That stabilizing respiratory control is important is illustrated by two studies that documented the position dependency of periodic breathing/central sleep apnea. Sahlin et al studied 20 consecutive patients with Cheyne-Stokes breathing.[8] Of these, 18 had congestive heart failure and two had suffered strokes. The mean central AHI fell from 41 ± 13 in the supine position to 26 ± 12 in the nonsupine position. The position dependency of central sleep apnea was confirmed by the study of Szollosi et al who also studied 20 patients with heart failure.[9] Both sleep stage and posture effected event frequency, but a

change to the lateral position significantly reduced the AHI (about 80% central events) to less than half the supine value in all sleep stages. The reduction in AHI was accompanied by a reduction in the magnitude of hypoxemia in the nonsupine position while event duration did not change. The authors concluded that changes in loop gain rather than an increase in upper airway collapsibility was the likely cause of the supine increase in AHI.

Efficacy of Position Restriction Therapy

Several investigations have studied the efficacy of positional therapy. Cartwright et al were among the first to investigate positional therapy using a position activated audio alarm to train patients to avoid the supine position.[10] In her subsequent study of sixty patients, over half reduced their AHI within normal limits and learned to avoid supine sleep.[11] The device used to detect supine sleep maintained a digital count of the number of times the alarm was sounded. More recently, a soft vest attached to a board placed under the pillow (a device called the Positioner) was developed to make it impossible for the patient to sleep supine. The device provided significant improvements in RDI, percent SpO_2 below 90%, snoring time, arousal index, and Epworth Sleepiness Scores (ESS, see Appendix B); long-term compliance, however, was low because of the discomfort caused by the vest.[12] Loord et al also evaluated the Positioner and reported that AHI and ESS decreased, whereas snoring increased in about half of the patients.[13] Patient tolerance and discomfort were again reported as a major limitation.

The "tennis ball technique" (TBT) was also evaluated in positional OSA patients for a period of 6 months by Oksenberg et al.[14] Of those who completed the study by completing a questionnaire, 38% continued to use TBT, 24% stopped using TBT after a few months but had learned to avoid the supine position, and 38% were noncompliant (ie, stopped using TBT and continued to sleep supine). Noncompliant patients were younger than compliant patients. The main reason cited for patients discontinuing TBT was discomfort.

Positional OSA treatment could have important therapeutic benefits for other comorbid diseases as well. For example, positional OSA was a predominant feature in acute stroke with its incidence decreasing significantly during the months following the onset of neurologic symptoms.[15] In another study, 63% of patients with acute ischemic stroke spent their entire time supine.[16] As noted above, two studies have found that sleep in the lateral position significantly attenuated the severity of central sleep apneas and AHI. In another study by Berger et al, after one month of treatment of positional OSA patients using TBT, all patients had a reduction in 24-hour mean blood pressure combined with a significant drop in mean 24-hour and mean awake systolic/diastolic blood pressure.[17]

Finally, there is a positional influence on other therapies for sleep apnea. Several investigators have found that continuous positive airway pressures needed to treat OSA are significantly less in the nonsupine versus the supine position.[5,18] The effectiveness of oral appliance therapy also is strongly influenced by sleep posture, and having positional sleep apnea is a significant predictor of success with mandibular advancing devices.[19,20]

In summary, as the above studies have shown, position restriction therapy is relatively easy to implement and has a reasonable level of effectiveness, especially

in patients with mild to moderate OSA (Table 17–1). As with most other treatments of OSA, the challenge lies in having patients continue using this therapy on a long-term basis.

NASAL EXPIRATORY POSITIVE AIRWAY PRESSURE (EPAP)

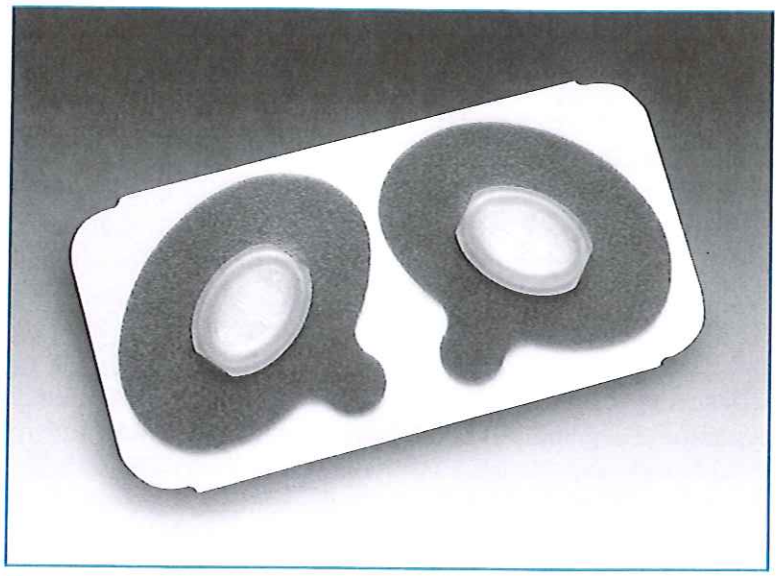
Nasal EPAP refers to the application of positive pressure to the airway only during the expiratory phase. The first experimental use of EPAP to treat obstructive sleep apnea dates back to 1983, when Mahadevia et al demonstrated in a small study of nine subjects that passive application of 10 cm H_2O of EPAP could lead to statistically significant improvements in apnea index, oxygen desaturation index, and mean oxygen saturation.[21] More recently, the first nasal EPAP device (Provent Sleep Apnea Therapy, Ventus Medical, Belmont, California) has become commercially available (Figs 17–2A and B). Indicated for the treatment of obstructive sleep apnea, this disposable device consists of a small one-way valve that attaches over each nostril and is secured in place with adhesive. The valve opens during inspiration and closes during expiration, redirecting expired air through small holes thereby creating resistance and expiratory positive airway pressure (EPAP). This EPAP has been shown to maintain positive pressure inside the airway through the start of next inspiration.[22]

Mechanism of Action

Traditionally, much of the investigative focus of pharyngeal obstruction during sleep has been on inspiration, when the force generated by the diaphragm lowers intraluminal pharyngeal pressure, promoting airway collapse. Yet as early as 1983, Sanders and Moore showed that in subjects with OSA, airway obstruction was present during both inspiratory and expiratory phases of ventilation, and that expiratory resistance increased progressively and significantly prior to an apnea,[23] a finding that has been confirmed in several subsequent studies. Importantly, the site of increased expiratory resistance (greatest decrease in area) is retroglossal and supraglottic.[24] In contrast, during inspiration,

TABLE 17–1. Clinical Pearls for the Use of Position Restriction Therapy

1. 65% of all patients with an overall AHI in the range of 11 to 40 will show at least a 50% reduction in AHI if the supine position is avoided.
2. If the overall AHI is 20 or less, then almost 50% of patients will have a nonsupine AHI of 10 or less.
3. Position restriction therapy should be strongly considered alone or in addition to other therapy especially in patients with proven positional sleep apnea or in those with overall mild to moderate OSA.
4. All diagnostic test methods should record sleeping posture.



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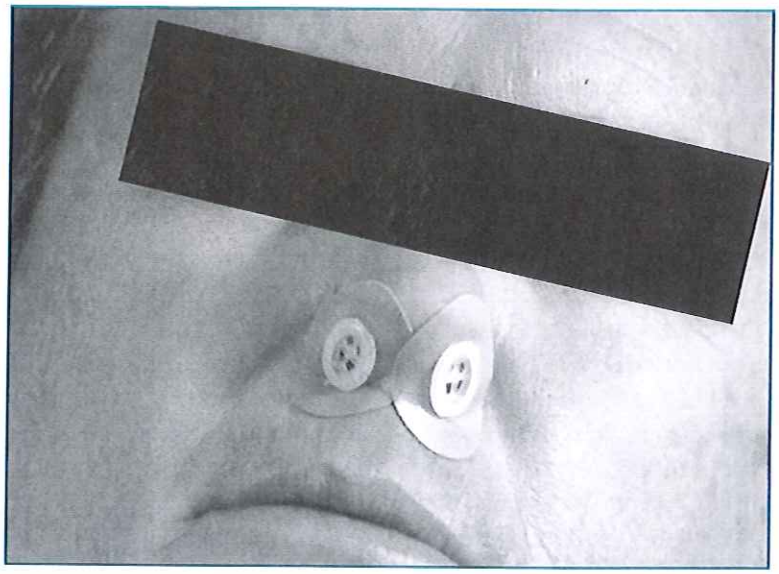

B

Fig 17–2. A and **B.** The Provent nasal EPAP device. This nightly use, disposable device consists of a small one-way valve that attaches over each nostril and is secured in place with adhesive. Reprinted with permission from Ventus Medical, Inc. Copyright 2009.

the most common site of airway collapse is retropalatal.[25] Furthermore, Morrell et al demonstrated a progressive fall in retropalatal cross-sectional area over the four breaths preceding an obstructive apnea, with the smallest cross-sectional area

present at end-expiration.[26] The authors conclude that, "pharyngeal occlusion is due to a combination of inspiratory and expiratory narrowing, with the latter rendering the lumen vulnerable to complete collapse during the subsequent inspiratory effort." The importance of expiratory pharyngeal narrowing in OSA is supported by the finding that inspiratory positive airway pressure (IPAP) alone may fail to open the airway, and that a critical level of expiratory positive pressure is required to prevent inspiratory flow limitation.[27-30]

The mechanism through which EPAP prevents pharyngeal collapse is still unclear, although multiple ongoing mechanistic studies with the Provent EPAP device promise to provide insight. Several mechanisms are possible and may act in parallel. First, it is known that positive expiratory pressure increases end expiratory lung volume (EELV) or FRC during sleep. An increase in FRC is associated with decreased pharyngeal compliance and an increase in upper airway size, making it more resistant to collapse. The increase in pharyngeal stiffness is independent of the method of increasing FRC, be it raising airway pressure or lowering body surface pressure.[31] A recently reported study demonstrated that an increase in lung volume alone significantly decreases sleep-disordered breathing and improves sleep architecture.[32] The primary mechanism is thought to be caudal traction on the pharyngeal airway.[31,32] However, EPAP also variably increases the activity of the upper airway dilator muscles, unlike CPAP which causes a marked decrease in the activity of these muscles.[33] An alternative explanation is that due to the increase in end expiratory airway pressure, the airway is larger at the start of the next inspiration, and this would decrease resistance to flow and thus collapsing pressure. In other words, an airway that is already patent at the end of expiration is less likely to collapse because it is already open.

Two recent studies of the Provent EPAP device help elucidate the mechanism of action. In the first, Colrain et al studied the use of a sham EPAP device (without a functioning valve) compared to an active EPAP device in nine subjects over multiple nights of in laboratory study.[34] The sham EPAP device was shown to impact neither AHI nor oxygen desaturation index (ODI), whereas the active EPAP device led to statistically significant reductions in both indices. Furthermore, according to a personal communication with Ian Colrain, PhD, the use of the active EPAP device was shown to eliminate the end expiratory pause when an analysis of respiratory timing was conducted during stable stage 2 sleep. In a second study, Hwang et al demonstrated that among responders to nasal EPAP, the end expiratory pressure (as measured intranasally) was dramatically higher than the end expiratory pressure measured in nonresponders to nasal EPAP.[22] This finding was interpreted as suggestive of the effect of increased traction of the trachea due to increased end expiratory lung volume.

Efficacy of Nasal EPAP

At least six studies have been completed to demonstrate the efficacy of the Provent EPAP device in the treatment of OSA. Data from the first two studies have been published and are summarized here. Colrain et al were the first to demonstrate the utility of using the Provent EPAP device in the treatment of OSA.[35] In this pilot study, 24 subjects with OSA underwent two

nights of in laboratory polysomnography, one night wearing the device and a second night without the device, with order of nights counterbalanced to minimize "first night effect." The polysomnograms were then scored by a blinded reader. The AHI ($p < 0.001$), ODI ($p < 0.01$), percentage of the night spent > 90% saturation ($p < 0.05$) were all improved significantly. Sleep architecture remained unchanged and snoring (as assessed by a piezo sensor) was significantly reduced ($p < 0.001$). Subjectively, the majority of the subjects found the device comfortable and all subjects who had prior experience with CPAP found the nasal EPAP device more comfortable than CPAP.

Rosenthal et al[36] subsequently reported on 34 subjects with OSA who used the Provent EPAP device over a 30-day period. In laboratory polysomnograms were administered prior to the use of the device at home and after 30 days of in home use. The AHI was reduced significantly both during the initial nights of study ($p < 0.001$) and after 30 days of home use ($p = 0.001$). Epworth Sleepiness scores decreased from 8.7 at baseline to 6.9 ($p < 0.001$) at 30 days. The Pittsburgh Sleep Quality Index also improved from 7.4 at baseline to 6.5 ($p = 0.042$) at 30 days. Mean oxygen saturation improved significantly at the end of 30 days ($p = 0.003$) as did percent of the night snoring ($p = 0.013$). Similar to the pilot study, sleep architecture remained unchanged from an essentially normal baseline. Importantly, the subjects in the study self-reported using the nasal EPAP device the entire night on 94% of possible nights. It should be noted that this compliance was based on self-report in nightly diaries as no objective means of assessing compliance was possible in the home setting.

Pooled efficacy data from the 58 subjects in the Colrain and Rosenthal studies shows that nasal EPAP reduced mean AHI from 26.6 ± 24.8 to 13.7 ± 20.1, a 49% reduction ($p < 0.001$). During treatment with nasal EPAP, 36% of subjects (21/58) had an AHI < 5, 59% of subjects (26/44) had an AHI < 10, and 66% of subjects (38/58) had an AHI improvement > 50% compared to baseline. Furthermore, 72% of subjects (42/58) met either the treatment AHI < 10 or AHI improved by > 50% criteria, and 50% of subjects (22/44) met both the AHI < 10 and AHI improved by > 50% criteria.[37] (Table 17-2 and Fig 17-3). It is important to note that in each of the above published studies, subject response was somewhat heterogeneous. This underscores the need for the physician to continue to follow those patients that are prescribed nasal EPAP to ensure a satisfactory result.

In summary, the use of the Provent EPAP device has been shown to lower AHI and offer compelling patient compliance based on early clinical studies (Table 17-3). Additional studies with larger numbers of subjects are currently underway and will provide longer term efficacy and compliance data, including studies lasting 3 and 12 months. Data from these long-term studies will provide physicians additional guidance on how to best utilize this new therapeutic option.

Notes: Rajiv Doshi, MD is Founder and Chief Scientific Officer of Ventus Medical, Inc., the maker of Provent Sleep Apnea Therapy. He receives a salary from and owns stock in the company.

Philip Westbrook, MD is Chief Medical Officer of Ventus Medical, the maker of Provent Sleep Apnea Therapy. He receives a salary from and owns stock in the company.

TABLE 17–2. Analysis of Apnea/Hypopnea Index by OSA Severity

	N	Mean	Median	Min to Max	STD
Mild OSA (control night 5 < AHI ≤ 15)					
Control	23	9.4	9.0	5 to 15	3.79
Treatment	23	5.8	4.2	0 to 22	5.18
Treatment-Control	23	–3.6	–4.1	–12 to 16	6.41
Moderate OSA (control night 15 < AHI ≤ 30)					
Control	20	19.6	17.7	15 to 30	4.12
Treatment	20	7.7	6.3	2 to 24	5.63
Treatment-Control	20	–11.9	–13.5	–27 to 7	7.72
Severe OSA (control night AHI > 30)					
Control	15	62.4	56.6	31 to 105	23.28
Treatment	15	33.8	20.9	2 to 101	31.22
Treatment-Control	15	–28.5	–26.2	–71 to 6	21.11

From pooled data from the Colrain et al[35] and Rosenthal et al[36] nasal EPAP studies (Courtesy Ventus Medical, Inc.)

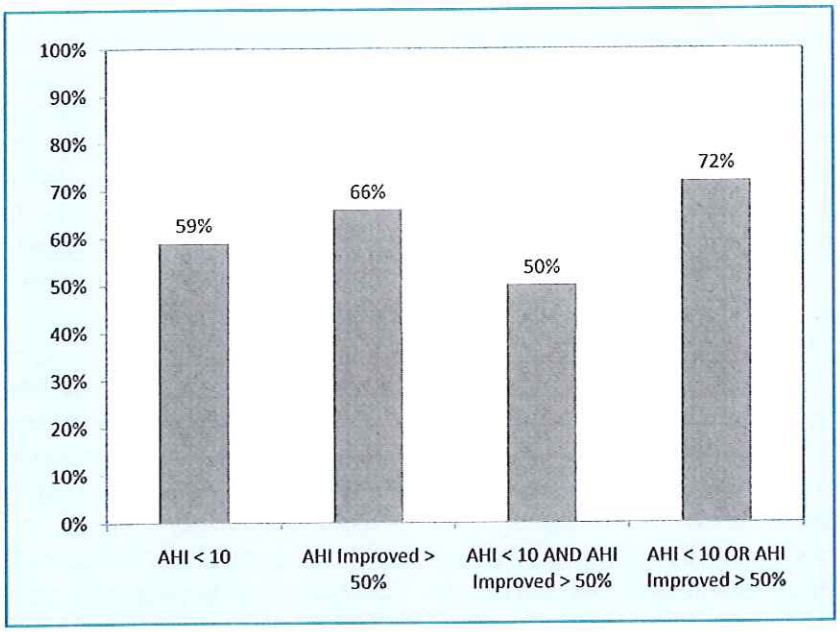

Fig 17–3. Percentage of subjects who achieved established therapeutic success criteria for AHI reduction. Data uses pooled subject data from the Colrain et al[35] and Rosenthal et al[36] nasal EPAP studies.

TABLE 17–3. Clinical Pearls for the Use of Nasal EPAP

1. Nasal EPAP has been shown to be effective in the treatment of mild, moderate, and severe OSA.
2. Response to nasal EPAP can vary from patient to patient. It is therefore important to provide adequate follow-up to ensure a satisfactory result.
3. Acclimating to nasal EPAP can take several days to a week or longer. It is important to set expectations with the patient before therapy is begun.

Dr. Westbrook also serves as Chief Medical Officer of Advanced Brain Monitoring, Inc., the maker of a portable sleep monitor. He receives a salary from and owns stock in the company.

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