CPAP and Bi-level PAP Therapy: New and Established Roles

Andreea Antonescu-Turcu MD and Sairam Parthasarathy MD

Introduction
Continuous Positive Airway Pressure Therapy
Bi-level PAP Therapy
Clinical Evidence for CPAP and Bi-level PAP
Modification of Expiratory Pressure Contour
Auto-titrating PAP Therapy
Scientific Evidence for Auto-PAP Therapy
Advanced Methods of Titration
Other Titration Methods
Summary

Over the past few decades, continuous positive airway pressure (CPAP) therapy for obstructive sleep apnea has evolved into more and more sophisticated modes of therapy for various forms of sleep-disordered breathing. While the principles of splinting the airway and delivering assisted ventilation underpin the basics of this therapy, the introduction of newer technologies and miniaturization are revolutionizing the former conventions of the field. The purpose of this review is to improve our understanding of various forms of PAP therapy by providing the rationale for such modalities, gaining a basic working knowledge of device technology, and critically assessing the clinical research evidence while identifying barriers to implementation. Dissemination of such information is vital in order to prevent knowledge gaps in healthcare providers and systems. Key words: obstructive sleep apnea; continuous positive airway pressure; adherence; adult; pediatric; compliance; sleep apnea; artificial respiration; central sleep apnea; servo ventilation; obesity. [Respir Care 2010;55(9):1216–1228. © 2010 Daedalus Enterprises]
connected to the trachea by a small tube. However, the introduction of positive-pressure ventilation into modern medicine did not occur until the disastrous polio epidemic in the middle of last century. In 1953, Bjorn Ibsen, an anesthesiologist, used bag ventilation connected to a tracheotomy to resuscitate a teenage girl suffering from respiratory failure due to bulbar poliomyelitis, and thereby gave rise to the concept of the modern intensive care unit. However, the noninvasive application of positive airway pressure to treat obstructive sleep apnea (OSA) had to await the nifty invention of a reversed vacuum machine by Colin Sullivan in 1981. Modern-day devices are getting to be much more sophisticated than a mere reversal of the vacuum pump. The purpose of this review is to improve our understanding of various forms of PAP therapy by providing the rationale for such modalities, gaining a basic working knowledge of device technology, and critically assessing the clinical research evidence while identifying barriers to implementation. Dissemination of such information is vital in order to prevent knowledge gaps in healthcare providers and systems.

Continuous Positive Airway Pressure Therapy

Continuous positive airway pressure (CPAP), as the name implies, requires the airway pressure to be constant between inspiration and expiration. Most often, such a pressure is achieved by a servo-controlled air compressor that maintains the airway pressure as closely to the prescribed pressure despite the pull (inspiration) and push (exhalation) of the patient (Fig. 1). The maintenance of such pressure within an FDA-specified pressure range (for example, ± 1.5 cm H₂O of the set pressure) is necessary as a quality-assurance measure that would ensure that the device maintains a certain prescription pressure for the patient. Such a pre-specified error range is generally greater with larger tidal volume (VT) or inspiratory effort from patient, faster respiratory rate, and at higher prescription pressure settings, because the device would need to be more rapidly responsive to the perturbations in the airway pressure at such extremes to maintain the pressure at the prescribed level. Modern day CPAP devices are more compact, primarily due to miniaturization of the controllers and electronics, but a limit is being posed by the work-output or wattage and therefore size of the air compressor.

Physiologically, the CPAP device works to splint the airway open and prevent the collapse of the upper airway that is the cardinal event of OSA (Fig. 2). Besides such a beneficial effect, there are other physiological benefits to CPAP: greater end-expiratory lung volume and consequent increase in oxygen stores and increased tracheal traction to improve upper airway patency and lower cardiac afterload and consequent increase in cardiac output (see Fig. 2). Conversely, CPAP may decrease venous return, increase abdominal muscle effort, provoke anxiety in susceptible individuals, and propagate central apneas by destabilizing breathing. In some patients, the administration of CPAP
may eliminate CO₂ and reduce arterial P̄CO₂ below the apnea threshold, and consequently lead to ventilatory instability characterized by central apneas and periodic breathing. Other side effects may be attributable to mask interface-related skin changes (abrasions, pressure sores, contact dermatitis, etc), aerophagia, sinus pain, oral and nasal dryness, and even tooth decay. Despite such side effects, CPAP may be one of the most cost-effective and least toxic form of medical therapy.³

In the real world, the implementation of CPAP technology involves many variables that may ultimately determine the success of the therapy. Many questions can be raised. How do we determine the adequate pressure? How do we titrate the pressure? What mask interface do we use? Do we use a humidifier? Should we set ramp feature? If so, at what level? How soon should we measure adherence to therapy? When should the patient follow up? How do we monitor the quality of services provided by the durable medical equipment provider? When and how often should we re-titrate the pressure setting? How do we prevent non-adherence to CPAP? How do we promote adherence to therapy? What are the determinants of non-adherence? And who is at greatest risk for non-adherence? How should the multidisciplinary healthcare providers work as a team to improve quality of service? The questions are innumerable, and the answers to some of these are in the companion papers in this Journal Conference.

Titration of CPAP level can be effected manually by a sleep technician attending an overnight polysomnography (PSG, the accepted standard), automatically by an auto-titrating device, calculated with formulas based upon OSA severity and neck circumference, or even self-titrated by the patient or bed partner. There has been no uniform method for titrating the CPAP level; however, a recent consensus statement begins to address this issue.⁴

There is general consensus with regard to the end points that dictate the upward titration of CPAP level: obstructive apneas, obstructive hypopneas, severe flow-limitation, or respiratory-event-related arousals and snoring.⁴ A respiratory-event-related arousal is defined as a reduction in air flow with progressive increase in effort, terminated by an arousal, in the absence of the required concomitant ≥ 3% reduction in oxygen saturation, measured via pulse oximetry. There is also general consensus that the pressure target should achieve a reduction in respiratory disturbance index (RDI, which is calculated as the number of apneas, hypopneas, and respiratory-event-related arousals divided by the duration of sleep time in hours) to less than 5 events per hour.⁴ Such a target pressure is considered “optimal” if at least 15 min of supine rapid-eye-movement (REM) sleep are observed at the pressure setting when RDI remains < 5 events per hour.⁴ However, the increments and rate of climb of pressure needed to reach such a target value can differ from laboratory to laboratory. Alternatively, a “good” titration achieves an RDI ≤ 10 events per hour or a decline by 50% if the baseline RDI < 15 events per hour, and should include supine REM sleep that is not continually interrupted by spontaneous arousals or awakenings at the selected pressure. An “adequate” titration does not reduce the RDI to ≤ 10 events per hour but reduces the RDI by 75% from baseline (especially in patients with severe OSA), or one in which the titration grading criteria for optimal or good are met with the exception that supine REM sleep did not occur at the selected pressure. And lastly, an “unacceptable” titration is one that does not meet any one of the above grades of optimal, adequate, or good. A repeat PAP titration study should be considered if the initial titration does not achieve a grade of optimal or good and, if it is a split-night PSG study, it fails to meet American Academy of Sleep Medicine criteria (ie, titration duration > 3 h). Such consensus in terminology is vital so as to standardize the interpretation of titration studies across laboratories and institutions.⁴

There is consensus that potential candidates for PAP therapy should receive adequate PAP education, hands-on demonstration, careful mask fitting, and acclimatization prior to titration. But there is no consensus on how rapidly the pressure level should be raised and whether a downward exploration or titration should be attempted once a certain adequate pressure level is reached.⁴

Studies involving mask interfaces and humidification have not demonstrated consistent benefits; however, this may be because of regional and inter-individual differences.⁵ Special care must be taken to fit the patients with the appropriate size and shape of mask or nasal pillows. The choice of humidification (heated humidification in dry climates and cold pass-over humidifier in warm and humid environs), though dictated by local weather and patient preference, are vital to prevent oronasal dryness and consequent discomfort.

Close follow-up, using a nurse-led or respiratory-therapist-led program, to troubleshoot problems encountered while on CPAP and to manage the ensuing side effects, is vital for a successful outcome.⁴ The success or effectiveness of PAP therapy is undermined by poor adherence. While the “efficacy” of PAP therapy (ability to treat obstructive events of OSA in the laboratory under ideal conditions) has never been in doubt, the “effectiveness” (effect in everyday life) remains an important cause for concern. Such concerns are based upon a high proportion of adults (46–83%) and children with OSA being non-adherent to PAP therapy, with non-adherence defined as less than 4 hours of nightly use.⁶ Recent findings in the important area of adherence pertain to a large association study demonstrating that non-adherence to PAP therapy is associated with greater likelihood for cardiovascular morbidity and mortality.⁷ Factors consistently associated with non-adherence to PAP therapy include asymptomatic in-
individuals, nasal obstruction, low self-efficacy, lack of risk perception, and lower socioeconomic status. Care by certified specialists and accredited centers may be associated with better adherence, but needs to be replicated. Interventions such as cognitive behavioral therapy, intensive education and support, and reduction of nasal obstruction have been consistently shown to augment adherence to therapy. Whereas the benefits of device or interface modifications are less clear, there is a paucity of investigations addressing PAP therapy adherence in children.

Novel methods to promote adherence to PAP therapy include the administration of the sedative eszopiclone during the PAP titration night, which improved adherence to CPAP therapy in the intervention, as compared to the placebo group: 76% versus 60% of nights used and 4.8 hours versus 3.9 hours used per night, respectively. Another study from the same investigators revealed that a short course of eszopiclone during the first 2 weeks of CPAP improved adherence and led to fewer patients discontinuing therapy. Because, early patterns of adherence—within the first week or so—may predict subsequent adherence, efforts to favorably modify adherence should occur early during the course of initiation of CPAP therapy. While the administration of sedatives in the first 2 weeks is a promising method to promote adherence, the generalizability of such interventions from the closely monitored conditions of a research study to day-to-day practice needs to be carefully considered from a patient-safety standpoint. Specifically, patients who are non-adherent to CPAP therapy may continue to use sedatives and may be at increased risk for motor-vehicle accidents.

**Bi-level PAP Therapy**

Bi-level PAP therapy was originally conceived with the idea of varying the administered pressure between the inspiratory and expiratory cycles. Such a variable pressure setting would conceivably decrease the amount of pressure against which the patient exhaled, thereby decreasing abdominal muscle recruitment and consequent respiratory discomfort during the expiratory cycle (see Fig. 1). Moreover, during the inspiratory cycle the greater level of pressure assist would combat the inspiratory flow limitation suffered by the upper airway (see Fig. 1). An additional benefit with bi-level PAP is the greater $V_T$ and unloading of the respiratory muscles, when compared to CPAP. As such, the difference between the inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) could be considered as pressure support level that could augment the inspired $V_T$. This feature can be exploited to combat “non-obstructive” hypoventilation that may occur due to a host of conditions.

The implementation of bi-level PAP and some of the impediments to such therapy are very similar to that of CPAP delineated above. In adults, the maximum IPAP pressure setting for bi-level PAP is not to exceed 30 cm H$_2$O, and the minimum difference between IPAP and EPAP level should not be less than 4 cm H$_2$O. In general, a transition from CPAP to bi-level PAP is encouraged when the CPAP level approaches 15 cm H$_2$O. This is because exhaling against CPAP levels approaching 15 cm H$_2$O can be uncomfortable for most patients.

Despite such an innovative technology, the advantages offered by bi-level PAP therapy over CPAP from an adherence standpoint have been mixed at best. A recent systematic Cochrane database review concluded that bi-level PAP therapy was not superior to conventional CPAP therapy from an adherence standpoint.

The cycling of the device from the inspiratory (IPAP) to the expiratory phase (EPAP) and vice-versa may be triggered by the spontaneously breathing patient (spontaneous mode) or by a set respiratory rate programmed into the device (timed mode). The sensitivities or the triggering threshold for causing the device to cycle in the spontaneous mode may be based on pressure, flow-contour, hard-wired timing, or a proprietary combination of such measures. While the intricacies of such sophisticated engineering are beyond the scope of this review, it suffices to say that dysynchronous cycling between the patient and the device can be uncomfortable and could lead to hyperinflation and further dysynchrony. In some older devices the triggering sensitivities could be adjusted by the therapist or physician, but in most modern bi-level PAP devices for home use the technology has veered in favor of automation and higher levels of sensitivity. Similarly, the rate of pressurization from EPAP to IPAP level (the “rise time”) can be adjusted to climb more briskly or more slowly. Such a feature may need to be adjusted for individual patient comfort, but the physiological or clinical implications of such settings are less clear. Specifically, some reports suggest that a brisk response (or shorter rise time) may have some inherent oscillatory behavior that may set the stage for “emergent” central apneas. Emergent central apneas are apneas without respiratory effort that occur following PAP therapy initiation for OSA. However, the effect of rise time on emergent central apneas has not been demonstrated in clinical studies outside of mathematical or bench models.

The administration of a backup rate (timed mode) during bi-level PAP therapy may be considered under 2 circumstances. The backup rate could be considered in patients with alveolar hypoventilation, with or without chronic respiratory insufficiency (elevated arterial $P_{CO_2}$) of various etiologies, which is primarily aimed at increasing $V_T$ and resolving the hypoventilation. Another circumstance would be to treat central sleep apnea or prevent the appearance of
emergent central apneas in patients undergoing PAP therapy for OSA. In both cases, the choice of the backup rate seems arbitrary and is probably best guided by polysomnographic resolution of central apneas or persistent hypoxemia due to alveolar hypoventilation ($S_{pCO_2} < 88\%$ in the absence of obstructive hypopneas or apneas as an indirect measure of hypoventilation). In general, a backup rate set at 2 breaths below the patient’s spontaneous rate during calm wakefulness breathing with titration upwards at 2-breath increments can be considered.

Although one of the potential benefits of bi-level PAP is to improve adherence to therapy or “salvage” CPAP-intolerant patients, the clinical studies are mixed in this area of study. However, a recent 2-phase intervention program that employed standard interventions (such as treatment of nasal congestion, mask optimization, heated humidification, and education) followed by a change to either bi-level PAP or CPAP achieved improved adherence in patients previously noncompliant with CPAP. Systematic reviews suggest that bi-level PAP may not be superior to CPAP with regard to adherence to PAP therapy as a patient outcomes end point. However, a case can be made that while Ballard and colleagues carefully selected their patients after eliminating the confounders (such as nasal congestion), other investigators failed to provide such personalized medicine and therefore did not fully realize the potential benefits of bi-level PAP therapy.

Clinical Evidence for CPAP and Bi-level PAP

In patients with OSA the clinical evidence for CPAP and bi-level PAP as therapy for improving the quality of life, self-reported daytime sleepiness, motor-vehicle accidents attributable to OSA-induced sleepiness and hypertension is mounting. Specifically, compelling evidence suggests that PAP ameliorates sleepiness in patients with OSA. Motor-vehicle accidents are reduced in patients with OSA following the initiation of CPAP treatment. Results of large randomized controlled trials (RCTs) are awaited on the effect of PAP therapy on neurocognitive end points and cardiovascular mortality, but current observational studies suggest that PAP therapy would reduce mortality attributable to cardiovascular events. Similarly, bi-level PAP therapy has been shown to improve health-related quality of life in patients with obesity hypoventilation syndrome and amyotrophic lateral sclerosis. Bi-level PAP therapy may slow the decline of forced vital capacity and prolong survival in patients with amyotrophic lateral sclerosis.

Modification of Expiratory Pressure Contour

Modification to the expiratory pressure contour has lately been a popular method to promote patient comfort and achieve a physiological reduction in pressure during exhalation. Such a rationale stems from observations that a common complaint by those using conventional CPAP is that it is difficult to exhale against the positive pressure. Therefore, reducing the pressure during exhalation was thought to improve patient comfort and adherence (Fig. 3). There are 2 forms of such expiratory pressure contour modifications: one (C-flex) is based upon a proprietary algorithm that sequentially introduces a variable (3-level) physiological decrease in pressure during exhalation; the other algorithm produces 3 predictable nadirs in pressure reductions during exhalation (EPR). Such expiratory pressure modifications can be introduced during CPAP, bi-level PAP, or even auto-titrating PAP.

Early single-center studies suggested a favorable effect of expiratory pressure contour modifications on CPAP adherence. Dolan and colleagues, in an RCT, did not find any effects on adherence; however, they reported greater mask comfort reported by patients receiving expiratory pressure contour modification. However, a recently concluded prospective, multicenter, double-blind study did not reveal a difference in adherence, side effects, or comfort levels. Nevertheless, in a subgroup analysis of a 3-month open-label study that commenced following study conclusion, patients in the conventional CPAP (control) arm had an improved adherence rate when they received pressure reduction during exhalation. Although the scientific evidence is not in favor of this device enhancement as a potential tool to improve adherence, such modifications afford “personalization” for the individual patient who is intolerant of PAP therapy.
Auto-titrating PAP Therapy

Devices with in-built microprocessors for detection and treatment of events of OSA have been called self-adjusting, automatic, auto-adjusting, smart CPAP, and auto-titrating PAP (auto-PAP). The purposes of auto-PAP devices was to serve as an alternative to in-laboratory manual titration; to achieve lower mean pressures that may, in turn, promote adherence; and for effecting changes in CPAP levels in response to changes in severity of OSA that occur following changes in weight, sleep state, body position, and alcohol ingestion. Lately, the purpose of automation has expanded to detecting sleep-disordered breathing (SDB), treating central apneas, and correcting hypventilation.

The auto-PAP devices have evolved over multiple generations that comprise enhancements to the sensing of SDB events (sensors), automated computing and analysis of the sensed signals (analysis), and a hierarchal set of algorithms that will determine the action taken by the auto-PAP device in response to the conditions exposed (effectors).

In the first generation of auto-PAP devices, the sensors merely measured pressure vibrations that were caused by snoring (Fig. 4). The next generation of auto-PAP devices were able to sense flow-based changes such as apnea, hypopnea, or inspiratory flow limitation, based upon the inspiratory flow contour (ie, flattening of the inspiratory flow waveform). More recent devices can differentiate central from obstructive apneas (using forced oscillation technique or measuring compliance changes following rapid injection of air); identify Cheyne-Stokes respiration (by detecting breath-by-breath variation in peak flow); identify hypventilation (by measuring $V_T$ or $V_E$ using calibrated flow sensors); compensate for air leaks (using sophisticated flow-based algorithms); and measure both upper and lower airway resistance (using forced oscillation techniques). Such signals are computed and analyzed instantaneously by a built-in microprocessor with a hierarchical set of algorithms that determine the device response.

Auto-PAP devices may increase the pressure in response to events such as obstructive apneas or obstructive hypopneas. Some devices are programmed not to increase the pressure beyond an arbitrarily identified pressure if the apneas do not respond to pressure changes in a predictable fashion (ie, change from apneas to obstructive “flow-limited” hypopneas). Other devices can be programmed to not increase the pressure in response to non-obstructive hypopneas (namely, hypopneas without inspiratory flow limitation or flattening of the inspiratory flow curve).

Newer generation devices can differentiate obstructive from central apneas and thereby be programmed not to raise pressure in response to central apneas, but to increase the pressure only in response to obstructive apneas. Algorithms are designed not only to increase but also to explore downward when there is a period of time with no respiratory events. Such algorithms are proprietary, and a provider should probably be well informed regarding the algorithms and how they influence the performance of auto-PAP devices before prescribing them.

The effector arm of the auto-PAP device has undergone changes as well. Newer generation devices cannot only increase the CPAP level, but can also increase the IPAP alone in order to ameliorate obstructive events (auto bi-level PAP), correct hypoventilation (averaged volume-assured pressure support), or combat central apneas in patients with complex sleep apnea or CPAP emergent central apneas (servo ventilation). The servo ventilator may also introduce a backup rate to prevent central apneas, and even though they are not called auto-PAP devices, they function using similar principles and can be judged as the latest generation of auto-PAP devices.

Scientific Evidence for Auto-PAP Therapy

The scientific evidence governing auto-titrating and other alternative methods for titrating PAP devices continues to evolve. Both bench and clinical studies need to be considered in assessing such auto-titrating methods, but only clinical trials with measured benefits to patient outcomes should guide practice.

Many bench studies have been performed comparing the devices made by different manufacturers across different generations of devices. Such studies have consistently shown that for a given set of events or conditions that characterize OSA, the responses of devices from different manufacturers are quite varied. One particular study demonstrated the scatter in pressure response of 4 older-generation auto-PAP devices to be as wide as 10 cm H$_2$O.
Such changes may be attributable to the auto-PAP device’s ability to sense the event or the algorithms that govern the device response. Moreover, bench studies have shown that air leak deleteriously affected the performance of auto-PAP devices, and that some devices were more resilient to air leak than others. Despite such bench studies, there are currently no published clinical studies that have identified the clinical implications of the effects of air leak on auto-PAP device performance. Clinical studies involving patients are needed to confirm the findings of bench studies instead of extrapolating bench data to the clinical realm.

A large body of clinical trials aimed at assessing the efficacy of auto-PAP and other alternative methods to titrate auto-PAP devices have accumulated over the past decade. We will primarily focus here on publications from RCTs. It should be noted that most of these RCTs recruited CPAP-naïve patients with moderate to severe OSA and avoided comorbid conditions that would deleteriously affect performance of auto-PAP devices. Some of the exclusionary criteria were nasal obstruction, morbid obesity with hypoventilation, history of palatal surgery, central sleep apnea, co-existent heart failure, or COPD.

In a large European study, Masa and colleagues randomized 360 CPAP-naïve patients to either auto-PAP, CPAP titration during full-night PSG, or a prediction-formula-based CPAP level in a multicenter RCT. In that study, auto-PAP was initiated at home after the patient received instructions and mask fitting in an out-patient setting. Over a 3-month period, improvements in subjective sleepiness, disease-specific health-related quality-of-life measures, and apnea-hypopnea index (AHI) were similar across the groups. There was no difference in adherence to CPAP treatment or the dropout rates during the follow-up period. Some general health-related quality-of-life measures that were not tailored for assessing patients with SDB improved to slightly less in the auto-PAP group, when compared to the PSG-based or formula-based methods for determining treatment CPAP level (effect size ≤ 0.5).

Another recent study identified patients with OSA using either PSG or limited PSG, and subsequently randomized the subjects and crossed them over to receive either auto-PAP or PSG-derived CPAP therapy. Patients in the auto-PAP group reported greater improvement in subjective sleepiness and greater objective evidence of PAP adherence, albeit such differences were small and their clinical benefits are unclear. In this rather large study, involving over 180 patients, objective measures of vigilance (Osler test) and health-related quality of life were not different in the 2 groups. Study limitations included issues surrounding the crossover design (namely a strong order effect), a short (6-week) assessment period, and perhaps a failure to choose a patient population most likely to benefit from auto-PAP therapy.

Other investigators, however, did select and study patients who were more likely to benefit from auto-PAP therapy, namely patients with a high within-night variability in auto-PAP-titrated pressure levels. Despite doing so, they failed to demonstrate any difference in PAP adherence or mean pressure levels when compared to the PSG-derived CPAP trial. Although subjective ratings for sleepiness were better following auto-PAP therapy, such improvements were not clearly explained by group differences in pressure or adherence levels. Similarly, Massie and colleagues selected patients requiring a CPAP pressure level of ≥ 10 cm H2O, and reported that auto-PAP therapy resulted in greater improvements in health-related quality of life and self-reported sleep quality than conventional laboratory PSG-determined fixed CPAP pressure.

One study, however, reported auto-PAP therapy failed to reduce AHI as much as conventional PSG-derived CPAP settings. In that study by Patruno and colleagues, blood pressure and insulin resistance improved to a lesser degree in the auto-PAP group, when compared to the group receiving conventional PSG-derived CPAP therapy. Interestingly, the study had rather lenient exclusion criteria that did not exclude patients with important comorbid conditions.

In a study employing auto-PAP device technology, 100 recently diagnosed patients with OSA were randomized into 4 groups (n = 25 each) and received standard or intensive home support plus either auto-PAP or CPAP. Adherence to therapy achieved by intensive home support with monthly home visits over a 6-month period was better than the relatively more expensive auto-PAP device technology. Moreover, considering the expenditure of provider time in issuing auto-PAP, downloading and interpreting the auto-PAP device output, and monitoring patients following initiation of auto-PAP therapy, cost-effectiveness analysis of auto-PAP therapy versus conventional treatment methods is direly needed in order to justify their use.

Forced oscillation technology has been used to measure upper airway impedance. A proposed advantage of such technology would be the ability to determine whether the upper airway is open or closed, and thereby prevent inappropriate increments in pressure during central events with an open airway. An RCT with 38 patients compared forced oscillation-technology-based auto-PAP versus laboratory PSG-derived CPAP and found that the pressure recommendations between these 2 methods were comparable and achieved similar reductions in AHI and self-reported sleepiness over a 6-week period.

The use of auto-PAP therapy in patients who have not previously undergone conventional PSG for establishing the diagnosis of OSA has also seen tremendous growth. Berry and colleagues performed an RCT wherein patients underwent portable testing for OSA based upon a tonometry- and actigraphy-based system. In 106 patients with...
daytime sleepiness and a high likelihood of OSA, administration of auto-PAP versus PSG-derived CPAP did not result in any differences in adherence to PAP therapy, improvement in sleepiness, improvement in health-related quality of life, or patient satisfaction. Although limitations included the possibility of being under-powered to show group differences, and a population that was all male with high pre-test probability for OSA, the study highlighted the ability of auto-PAP to achieve benefits comparable to PSG-derived CPAP when used with home study testing without electroencephalography.\textsuperscript{51}

In another study that did not use PSG for diagnosis of CPAP titration, Mulgrew and colleagues found that PSG-derived CPAP titration did not confer any advantage over auto-PAP therapy initiated following identification of OSA by a clinical paradigm that involved the sequential application of the Epworth Sleepiness Scale score, Sleep Apnea Clinical Score, and overnight oximetry.\textsuperscript{52} In fact, the patients randomized to auto-PAP were more adherent to PAP therapy than those in the conventional PSG-derived CPAP pressure group.\textsuperscript{52} One limitation was the fact that the study was designed as a superiority trial, and large studies designed as non-inferiority trials are still needed. Another recent study has moved further down this aggressive path by using only a Berlin questionnaire to diagnose OSA in a population of United States veterans.\textsuperscript{53} Patients with a high likelihood of OSA (n = 109) who were awaiting diagnostic PSG were randomized to remain in the conventional pathway or assigned to auto-PAP therapy, which was initiated on an out-patient basis. In the study by Drummond and colleagues, in patients with 2 or more positive responses in the Berlin questionnaire, auto-PAP therapy improved self-reported symptoms and disease-specific health-related quality-of-life measures that were comparable to patients in the conventional group. A limitation to the generalizability of this finding is the high pre-test probability and all male population; 66% of eligible patients were excluded due to comorbid conditions such as heart failure and COPD.\textsuperscript{53}

Nurse-led home-based initiation of auto-PAP therapy in a large non-inferiority trial with 619 subjects (to date the largest published RCT involving auto-PAP therapy) demonstrated equivalence, compared to patients treated by sleep physicians using conventional PSG.\textsuperscript{54} In that study, Antic and colleagues also demonstrated lower costs in the nurse-led group.\textsuperscript{54} Such large non-inferiority trials need to be replicated in the United States for change in practice to occur.

Clinical comparisons between different auto-PAP devices have been made in a randomized controlled manner. In a crossover study design with 3 conditions and a one-month period of therapy, Senn and colleagues compared 2 different auto-PAP devices and CPAP therapy based on pressure level determined following 2 weeks of auto-PAP therapy.\textsuperscript{55} All 3 modalities achieved comparable improvements in symptoms, quality-of-life domains, and AHI. Séries and colleagues performed a similar trial with a 10-day washout period between 3 different auto-PAP devices. Each patient underwent therapy for a one-week home trial. They found that the median pressure during therapy with one manufacturer’s device (5.9 cm H\textsubscript{2}O) was significantly lower than that during therapy with the other 2 devices (7.4 cm H\textsubscript{2}O).\textsuperscript{56} Such clinical results parallel the bench-study findings of the precursor devices from the same manufacturers.\textsuperscript{54} Despite such differences between manufacturers, interestingly, in a survey of board-certified sleep physicians, only 37% of physicians who prescribed auto-PAP preferred a particular brand.\textsuperscript{57} Such findings may underscore the incongruence between scientific evidence and day-to-day practice and calls for better dissemination of study findings.

In summary, as long as patients are carefully selected, auto-PAP-derived optimal CPAP pressure compares favorably to PSG-derived CPAP determinations.\textsuperscript{58} Specifically, patients with important comorbidities such as heart failure, COPD, central sleep apnea, or hypventilation syndromes need to be excluded from such treatment strategies.\textsuperscript{58} While it may appear intuitive that auto-PAP therapy may provide cost savings, formal cost-effectiveness studies need to be performed in tandem with RCTs or across healthcare system databases. In general, the comparative-effectiveness of auto-PAP and PSG-based management strategies requires further study.

Advanced Methods of Titration

Advanced automation of devices that can identify and treat central apneas has been developed and is currently marketed. Servo ventilation can treat Cheyne-Stokes respiration, central sleep apnea, and emergent central apneas. The technology of this device involves a servo-controlled automatic adjustment of the pressure support level (effector) that is inversely related to the changes in peak flow over a moving time window (sensor) (Fig. 5). Specifically, if the peak flows are lower than the average peak flow derived from the previous moving time window, the device recognizes this as the decrescendo pattern that precedes a central apnea, and responds by increasing the pressure support level. Alternatively, if the peak flow is significantly higher than the average peak flow levels over the preceding moving time window, the device assumes that this is a hyperpnea, and reduces the level of pressure support. Therefore, the servo system dampens the inherent oscillatory behavior of the patient’s breathing pattern and smoothes respiration (see Fig. 5).

How does one set the servo ventilator? The EPAP is set to a level that can treat obstructive apneas and obstructive hypopneas and before central hypopneas manifest, but there may be some inter-observer variability in determination of such a pressure level (Fig. 6). Some investi-
gators believe that the EPAP level should not exceed 15 cm H₂O in patients with heart failure and central apneas, due to concerns surrounding decreased venous return and consequent hypotension in a preload-sensitive cardiac condition.

The IPAP level is determined instantaneously by the device algorithm (see above) within a pre-specified range prescribed by the physician (between the minimum and maximum IPAP [IPAP_min and IPAP_max]) so as to be able to provide variable pressure support (viz, pressure support = IPAP minus EPAP) (see Fig. 6). The IPAP_min is generally assigned as a value equal to the EPAP level or 2 cm H₂O above the EPAP level so that the minimum pressure support level can be 0–2 cm H₂O. In some devices, however, the difference between IPAP_min and IPAP is preset and the physician does not have to choose the minimum pressure support level. The maximum IPAP is not to exceed 30 cm H₂O. The backup rate can be set at automatic or can be set manually. In general, the backup respiratory rate is set 2 breaths below the patient’s spontaneous respiratory rate during calm wakefulness breathing, and titrated upwards if the patient manifests persistent central apneas during titration. Many studies have employed a backup rate of 15 breaths/min.39,59 Paw = airway pressure.

More recent servo ventilators incorporate auto-titration for determining the EPAP, which obviates having the physician pick the EPAP. This still requires physicians to set the EPAP range (EPAP_min and IPAP_max), just as they would with an auto-PAP device. These devices have in-built sophisticated proprietary systems that can distinguish between central and obstructive apneas. Such ability is crucial with regard to how the device should respond to an event. If the event were an obstructive event, conceivably the correct response would be to increase the EPAP setting, whereas if the event were a central “non-obstructive” hypopnea, the correct response would be to activate the servo mechanism and or increase the respiratory rate.
Small RCTs have shown that servo ventilation made by different manufacturers can successfully detect and treat central apneas.\textsuperscript{38,39,59,60} Such studies have involved patients with Cheyne-Stokes respiration and central sleep apnea\textsuperscript{38,39,59,60} or CPAP emergent central apneas.\textsuperscript{38} They have used manually set backup rates set at 15 breaths/ min,\textsuperscript{39,60} or employed an automatic backup rate.\textsuperscript{38,39} They have used EPAP levels of 5 cm H\textsubscript{2}O in patients with Cheyne-Stokes respiration and central sleep apnea\textsuperscript{39,60} or titrated the EPAP level to treat obstructive apneas in patients with emergent central apneas.\textsuperscript{38,39} Some of these studies have demonstrated improvement in objectively measured sleepiness and urinary measures of catecholamines in patients with Cheyne-Stokes respiration and central sleep apnea.\textsuperscript{60} However, large studies on the effects of such devices on other patient outcomes such as health-related quality of life, cardiac function, adherence to PAP therapy, and mortality are eagerly awaited. One study combined an auto-PAP device to a servo ventilator, with auto-PAP determining the EPAP level automatically, whereas the servo ventilation controlling periodic breathing and central apneas. This recent study by Randerath and colleagues reported such a combination of 2 devices to be effective in ameliorating SDB.\textsuperscript{61}

Advanced titration methods for patients with hypoventilation target minute ventilation (V\textsubscript{E}) and V\textsubscript{T} rather than events of SDB such as apneas and hypopneas (Fig. 7).\textsuperscript{36,37} Such devices assure a certain V\textsubscript{E} or target V\textsubscript{T}. These devices use the same platform as the bi-level PAP with built in automation. Unlike the auto-bi-level PAP device, which targets obstructive events like the auto-PAP, and the servo ventilator that targets central apneas and Cheyne-Stokes respiration, the volume assures pressure support devices target V\textsubscript{T} and/or V\textsubscript{E} (see Fig. 7). These devices require an EPAP level aimed at treating obstructive events, whereas the IPAP\textsubscript{max} and IPAP\textsubscript{min} are specified along with the target V\textsubscript{T}. The target V\textsubscript{T} is used at 8 mL/kg ideal body weight or 110\% of ambient V\textsubscript{T} during calm wakefulness. The operating IPAP level oscillates between the IPAP\textsubscript{min} and IPAP\textsubscript{max} in order to assure the target V\textsubscript{T}. The rationale for such an operation was to combat the hypoventilation in patients with obesity-hypoventilation syndrome, restrictive chest-wall disorders, and neuromuscular conditions such as amyotrophic lateral sclerosis.

In patients with obesity-hypoventilation syndrome it has been suggested that CPAP alone may be effective when administered alone or in combination with oxygen.\textsuperscript{62} However, that study may suffer from type 2 error, and, in fact, demonstrated evidence for greater improvements in subjective sleep quality and objective sleepiness measures in subjects receiving bi-level PAP, as opposed to CPAP therapy.\textsuperscript{62} Moreover, there were tendencies for better sleep quality in patients receiving bi-level PAP therapy, and such a finding was despite the fact that 20\% of potential subjects were excluded during screening because they failed CPAP therapy.\textsuperscript{62} A study from the same group suggested that greater obesity, substantial restrictive defect on pulmonary function testing, severe hypoxemia during sleep study, and higher arterial P\textsubscript{CO\textsubscript{2}}, during wakefulness were all associated with a higher likelihood for failure of CPAP.\textsuperscript{63} However, none of the aforementioned variables could predict patients in whom CPAP was to fail.

How do volume-assured pressure-assist devices compare to bi-level PAP therapy in patients with alveolar hypoventilation during sleep? While better ventilation and gas exchange have been observed, short-term studies using such advanced titration devices have so far failed to demonstrate advantages over conventional bi-level PAP settings with regards to improvements in sleep quality.\textsuperscript{36,37} Nevertheless, such volume assurance has advantages with regards to lower transcutaneous P\textsubscript{CO\textsubscript{2}} readings\textsuperscript{37} and greater V\textsubscript{E},\textsuperscript{36} but whether there are short- or long-term clinical benefits to patients is unclear.

**Other Titration Methods**

A small randomized single-blind 2-period crossover trial of CPAP treatment at the laboratory PSG-determined optimal pressure versus at-home self-adjustment of CPAP (starting pressure based on prediction equation) revealed comparable patient outcomes in both arms.\textsuperscript{64} The prediction formula was derived from readily available parameters, namely, body mass index, neck circumference, and AHI.\textsuperscript{65} Patients were subsequently encouraged to adjust the pressure as necessary to maximize comfort and perceived efficacy.\textsuperscript{64} Following the ensuing 5-week treatment period, adherence to PAP therapy, subjective and objective sleepiness, sleep apnea severity, and sleep architecture were all similar between the 2 groups. However, it was a small study. In a much larger aforementioned study, Masa and colleagues subjected one third of the patients...
to the prediction formula \[ \text{predicted pressure} = (0.16 \times \text{body mass index}) + (0.13 \times \text{neck circumference}) + (0.04 \times \text{AHI}) - 5.12, \] up to a maximum of 9 cm H$_2$O and the other 2 groups were either managed with the conventional laboratory PSG-derived pressure or auto-PAP derived pressure. Patients who exceeded a requirement of 9 cm H$_2$O based upon the formula were prescribed only 9 cm H$_2$O and asked to self-adjust the pressure upwards in 1 or 2 cm H$_2$O increments, based upon the observations of the bed partner. Although the CPAP level based on the predicted formula was slightly lower than that achieved by auto-PAP, the predicted formula achieved pressure comparable to the laboratory PSG-derived CPAP. There was no difference between all 3 groups with respect to AHI, subjective sleepiness, or PAP adherence levels. Other prediction formulas exist but have not been studied in an RCT.

**Summary**

The devices used to treat SDB continue to evolve rapidly. While the automation and simplification of settings are motivating the manufacturers to conceive and produce better devices, the future of such devices in day-to-day practice still rests in the hands of the individual prescribing physician, policy makers, regulatory bodies, and expert consensus. Future research needs to move the administration of PAP therapy from scientific evidence derived from randomized controlled trials to development and dissemination of comparative-effectiveness research that addresses the incorporation of such tools into the complex medical systems of healthcare delivery.

**REFERENCES**


61. Randerath WJ, Galteke W, Kenter M, Richter K, Schafer T. Combined adaptive servo-ventilation and automatic positive airway pressure (anticyclic modulated ventilation) in co-existing obstructive and

Discussion

Quan: Sai, the C-Flex [Respironics, Murraysville, Pennsylvania] on average doesn’t seem to help people improve adherence, but it seems like it is on almost every machine anyway. So why not take the opposite point that maybe we should set it on every machine because it’s there anyway?

Parthasarathy: Yes, I think it’s where cost-effectiveness comes into play.

Quan: Unless of course they make the machines cheaper.

Parthasarathy: I think it costs about $100 more, but I might be wrong.

Kapur: It shouldn’t be surprising to us that C-Flex doesn’t improve adherence in all patients, because that’s the same thing we found with auto-titraters, for which there’s limited evidence in some subgroups that it might help. So the finding that C-Flex does not generally improve adherence is not surprising.

On another topic, the lesson from the CanPAP [Canadian Positive Airway Pressure] Trial1 isn’t that CPAP shouldn’t be used any more for Cheyne-Stokes respiration. The follow-up analyses2 showed that the group that had a decrease in apnea-hypopnea index with CPAP had better survival. That supports a flow diagram in which if CPAP controls sleep-disordered breathing, keep them on CPAP, and if it doesn’t, then don’t and instead try adaptive support ventilation.


Mokhlesi: I have used adaptive servoventilators (eg, Maquet, Rastatt, Germany), though I can’t say I have extensive experience with them, and something I noticed was that on occasion I get outstanding response. The Cheyne-Stokes respiration goes away. But sometimes I notice that with the full face-mask I see a flow signal, so it looks like there are respirations, but the chest and abdomen signals don’t move. Have you seen that?

Parthasarathy: Yes.

Mokhlesi: What do you think that is? I’m not talking about people who have body mass indexes in the 60s, in whom one might see that the belt is not picking up the signal because of massive obesity with reduced chest and abdomen excursions. I have seen this in mildly obese individuals as well. Makes me wonder if the mask is creating this funny signal that is not real.

Parthasarathy: Two other people I’ve talked to mentioned observing that phenomenon. The mask flow seems to be showing a signal, but it’s not reflected in the effort signal. I speculate that it’s because of the backup rate that’s pushing in, and so you have essentially a closed upper airway. The patient has central apnea and the ventilator is administering positive-pressure breaths and the lungs are not being inflated, the airway is not open, the patient is actually “Cheyne-Stoking,” but the flow—if you made your hypopnea scorings just based on the flow tracing, you’re not going to score a hypopnea. This is just speculation; I’m not sure that that’s what happening. The American Academy of Sleep Medicine guidelines for scoring require that you look at all 3 channels: both the rib-cage and abdomen effort channels and the flow channel. To the untrained eye or someone who only looks at the flow and not the other 2 tracings, there is definitely a chance that such respiratory events could be missed.

Kuna: Since I’m holding the banner for portable monitoring at this meeting, I’d like to clarify something about auto-CPAP. The reason that practice guidelines exclude patients with chronic heart failure and COPD from portable-monitor testing is because the studies that have been done have all excluded those patients. Consequently, we lack the evidence supporting the use of diagnostic portable monitors and autoCPAP units in these special patient populations. It’s not that those patients developed problems. It’s that they have not been tested. We need to do those studies.
Parthasarathy: I totally agree. I don’t want to give the impression that I don’t believe in auto-PAP technology. We have a vibrant auto-PAP program and we use pulse oximetry and a home auto-PAP program. About a third of our patients qualify for the program. I think that’s a big cost saving and it alleviates the sleep lab’s backlog, so, again, I think it’s a very patient-centered and tailored approach of managing appropriate patients, until any evidence comes up to suggest otherwise.

I just wanted to point out some of the pitfalls, because in the physician survey we did we found that a third of the board-certified sleep physicians who responded were unfamiliar with the contraindications and exclusion criteria for auto-PAP. In fact, some physicians responded that auto-PAP technology could be used for managing central apnea. I have brought it up with the device industry that FDA approval process sets a higher bar for pharmaceuticals than for devices. Unlike the pharmaceutical industry, the device industry does not commit sufficient effort to perform head-to-head studies between devices or to adequately educate the professionals who will be prescribing the devices. I think there are lots of complexities and contraindications with these devices, and those need to be disseminated widely.

Gay: Sai, I think we ought to lend some credibility to your comments about complex sleep apnea. I’ll be the first to admit that it’s very controversial, but I think we should also mention that even Shahrokh Javaheri, with whom I’ve done pro-con debates, and Atul can admit there are some unique aspects about these patients. But there are some ways, as you point out, that you can provoke this disease. The argument about this being more common in split-night studies, and that it’s more likely to occur with over-titration with bi-level devices is supported by the Johnson and Johnson study,1 which suggested that you could do this very easily with overly aggressive titration.

What we noted in 20072 is the fact that this is a supine non-REM disease. There seems to be some patients who come back after their initial titration, and you’ll notice that the central apneas are still exacerbated by having them on their back, even at a lower CPAP level. Lowering the CPAP for central apnea should be a part of any titration. Patients should have the PAP pressure initially increased during titration, but the pressure should be brought down again to avoid the over-titration argument.

A trial that should be very insightful is the multi-center trial at Mayo,2 which includes folks from Illinois, where patients who have OSA at the baseline and then show during their initial exposure to CPAP (which has to be a minimum of 3 hours) that have persistent centrals more than 50% of the time are randomized to either CPAP or adaptive support ventilation. I hope that in a randomized trial format we’ll be able to get a better idea about the number of patients with persistent complex sleep apnea than what is all retrospective data that we have right now. Even Atul will admit that some people clearly fit that definition.


Parthasarathy: I agree. As I mentioned, my plan was to try to be provocative.

Gay: You succeeded.

Parthasarathy: But I still think the data need to be generated, to show that as a unique entity and to show patient outcomes. How can we improve patients’ lives or their heart conditions?

Patil: I was going to agree with Peter, in the sense that these patients with complex sleep apnea do exist, but I worry about the label being perpetuated within the general sleep community, because the label is overused. I think part of what we need to do in the RCT setting is to be more accurate in terms of the language defining this patient population, so that treatment strategies are applied to appropriately identified patients.

Quan: I’m glad you spoke up Peter, because the paper Sai quoted3 was one half of a pro-con debate, and I believe you wrote the other half.2 So I think if somebody is interested in hearing the other side of that argument, they should read both halves of the pro-con debate.

I’m struck by the fact that we have this technology, adaptive support ventilation, and even bi-level itself, and there’s this dearth of prospective RCTs showing any benefit. You had data3 showing that sometimes central apneas go away, but in any large prospective RCT I don’t see those data. And yet people are out there prescribing it willy-nilly all over the place.


Parthasarathy: Yes, and so the ADVENT-HF trial with the servo-ventilation device in heart failure and sleep apnea should be commencing.1


Quan: I congratulate Doug Bradley on starting that multi-center study; I think we need that.