Review Article

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Continuous positive airway pressure therapy: New generations

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Continuous positive airway pressure (CPAP) is the treatment of choice for obstructive sleep apnoea syndrome (OSAS). However, CPAP is not tolerated by all patients with OSAS and alternative modes of pressure delivery have been developed to overcome pressure intolerance, thereby improving patient comfort and adherence. Auto-adjustable positive airway pressure (APAP) devices may be utilised for the long-term management of OSAS and may also assist in the initial diagnosis of OSAS and titration of conventional CPAP therapy. Newer modalities such as C-Flex and A-Flex also show promise as treatment options in the future. However, the evidence supporting the use of these alternative modalities remains scant, in particular with regard to long-term cardiovascular outcomes. In addition, not all APAP devices use the same technological algorithms and data supporting individual APAP devices cannot be extrapolated to support all. Further studies are required to validate the roles of APAP, C-Flex and A-Flex. In the interim, standard CPAP therapy should continue as the mainstay of OSAS management.

Key words A-flex - auto-adjustable positive airway pressure (APAP) - C-flex - continuous positive airway pressure (CPAP) - obstructive sleep apnoea syndrome (OSAS)

Continuous positive airway pressure (CPAP) therapy was first described in 1981 by Sullivan *et al*[1] in a cohort of 5 patients with severe obstructive sleep apnoea syndrome (OSAS). It has since become the backbone of therapy in OSAS. Intermittent pharyngeal obstruction is the major pathogenetic mechanism in OSAS and CPAP therapy prevents this by acting as a "pneumatic splint" thus maintaining a patent airway throughout the respiratory cycle.

Epidemiological studies have demonstrated that OSAS is a largely unrecognised medical condition with profound health effects[2-4]. Treatment of OSAS with CPAP has been shown to have both physiological benefits as well as improving quality of life. Sleep architecture is improved with markedly increased slow wave and rapid eye movement (REM) sleep initially with CPAP therapy[5]. Excessive daytime sleepiness (EDS) is the most common symptom in OSAS and symptomatic patients have shown subjective and objective improvements in measures of daytime sleepiness with CPAP treatment[6]. Impairment in cognitive function, driving competence and psychosocial functioning is recognised in untreated OSAS patients and CPAP therapy has established efficacy in improving these parameters in symptomatic patients[7,8].

Patients with untreated OSAS are at increased risk for motor vehicle accidents and this risk is at least

reduced, if not removed, with CPAP therapy[9]. The major health risk in OSAS patients is the strong association with cardiovascular disease and long-term follow up studies of patients on CPAP therapy have also shown a significant benefit in reducing cardiovascular mortality and non fatal cardiovascular events[10,11].

Although CPAP is a highly effective therapy, its efficacy is dependant on regular usage and therefore adherence to therapy is of major importance. Average use is about 5 to 6 h per night in most compliant patients. After initial CPAP titration, about 80 per cent accept CPAP as continuing therapy[12,13].

Over the past 25 years, various features have been incorporated into CPAP devices, including ramps, automatic leak compensation and humidification, and the choice and sophistication of CPAP accessories such as masks has increased dramatically as efforts have been made to improve patient compliance. Although pressure intolerance is not the most common CPAP side effect, alternatives to, and variants of CPAP have also been developed to tackle this aspect of therapy to improve patient's comfort and adherence to therapy.

Auto-adjustable positive airway pressure (APAP)

Auto-adjustable positive airway pressure (APAP) devices are an emerging treatment alternative to fixed-pressure CPAP therapy for OSAS, aimed at delivering optimized pressure throughout sleep and making therapy more comfortable and tolerable. It has been postulated that patient compliance may be improved as a result although the premise that higher nasal pressures leads to poor CPAP compliance is not strongly supported by the literature[14]. APAP devices may also assist in the initial diagnosis of OSAS and help determine an effective level of fixed pressure for treatment with conventional CPAP, by detecting and recording respiratory disturbances without correcting them.

Upper airway resistance represents a dynamic property dependent on numerous factors, including body position, body weight, sleep stage, sleep deprivation, alcohol consumption and the use of other sedatives, nasal resistance and airway humidification[15-23]. Variation in these factors can occur within a single night or between nights causing changes in airway resistance. The level of fixed pressure required for effective treatment of OSAS has been shown to decrease during the first 8 months of therapy, presumably due to resolution of upper airway oedema with treatment[24]. Therefore, it is almost inevitable that prescription of a fixed single pressure, as employed in CPAP, will result in excessive pressures for parts of the night and suboptimal pressures at other times. APAP devices can automatically detect changes in surrogates of upper airway collapse and adjust the pressure delivered accordingly, allowing delivery of an optimal pressure throughout the night.

Detection of upper airway resistance by APAP

The sensors and algorithms employed to calculate the appropriate pressure to be delivered vary across APAP devices. Numerous markers of upper airway collapse such as snoring, apnoeas / hypopnoeas, flow limitation and the forced oscillation technique have been utilized in devices. Snoring is typically detected by analysing amplitude variation in the flow signal following band-pass filtering[25]. Various techniques have been used to detect apnoeas /hypopnoeas, including analysis of the pressure generated in the anterior nares through standard nasal cannulae, detection of differences between maximal inspiratory and expiratory flow and the use of pneumotachographs[26,27]. Several devices use a forced oscillation technique (FOT), detecting changes in airway impedance by superimposing an oscillatory flow to the airstream. This technique facilitates detection of upper airway collapse prior to physiological responses such as microarousals[28]. The characteristic flattening of the inspiratory airflow limb, which precedes an upper airway obstruction, may be the most sensitive sensor of upper airway obstruction[29,30]. Analysis of the inspiratory flow contour in this manner is used in a number of current devices [Autoset (ResMed, Sydney, Australia); Goodknight (Puritan Benett, Colorado, USA)].

Delivery of positive airway pressure by APAP

Most APAP devices operate in the range of 3 to 20 cm H_20 and the algorithms employed for pressure change vary considerably between devices. They all share the common goal, however, of aiming to deliver the lowest effective pressure required to alleviate upper airway obstruction and its consequences. Upon detection of a respiratory event, the pressure delivered is increased until an effective therapeutic pressure is reached. If no further respiratory abnormalities are detected, the pressure delivered reduces again at a pre-determined rate. In order to avoid arousals from sleep from abrupt alterations in pressure, changes are made gradually. The pressure delivered across devices and APAP algorithms differs[31] (Table).

Table. Comparison of compliance and pressure delivered across 3 APAP devices

	CPAP	RemStar Auto	Autoset Spirit	Breas Pv 10i
Nights used %	100 (94-100)	100 (79-100)	96 (42-100)	59 (17-93)**
Mean time used (h/night)	6.6 (5.9-7.9)	7.1 (5.3-8.1)	6.8 (5.9-8.0)	5.0 (3.8-5.6)**
Mean pressure cm H_20	10 (8-12)	7.3 (6.0-9.1)*#	8.0 (7.2-10.4)#	5.3 (4.5-6.8)**
Maximum pressure cm H_20	10 (8-12)	13.4 (9.4-16)#	12.2 (10.2-13.4)	10.2 (7.2-12.4)

Data are presented as median (interquartile range). CPAP, continuous positive airway pressure; APAP, auto-adjustable positive airway pressure

*P<0.05 versus Autoset Spirit; **P<0.01 versus CPAP, RemStar Auto and Autoset Spirit; #P<0.01 versus CPAP

Source: Ref. 31

Most studies assessing APAP have excluded patients with congestive cardiac failure and central sleep apnoea syndromes, individuals with significant lung disease such as chronic obstructive pulmonary disease (COPD), patients with obesity hypoventilation syndrome and other conditions associated with nocturnal arterial oxyhaemoglobin desaturation, and patients who did not snore[32]. Consequently, it is recommended that these patients are not candidates for APAP titration or therapy[32,33].

Use of APAP to diagnose OSAS

Currently, an estimated 80-90 per cent of OSAS remain undiagnosed. Yet, there was a 12-fold increase in annual diagnosis and reporting of OSAS in USA between 1990 and 1998[2]. The increasing recognition of OSAS and its consequences has resulted in substantial increase in the number of referrals to specialist sleep centres, which leads to lengthening waiting times for diagnostic sleep studies[34].

Traditionally, polysomnography (PSG) has been the "gold standard" for investigating patients suspected of having OSAS. This investigation, which involves monitoring of sleep stage in addition to respiration, gas exchange and other variables, continuously during sleep, is time-consuming, labour intensive, and requires continuous supervision of the patient and recorder during the course of the sleep study to achieve optimum results[35,36]. Further, the equipment used for PSG studies is expensive and there may also be a diminution of sleep time and quality due to the discomfort caused by the numerous electrodes attached to the patient[37].

The American Academy of Sleep Medicine (AASM) guidelines currently do not recommend the use of APAP devices for diagnostic purposes[32]. Only a few studies have examined the use of APAP in diagnosing OSAS. Most studies have directly compared APAP with concomitant PSG and have lacked uniformity in terms of patient selection across studies[38]. It should also be noted that PSG expresses apnoea-hypoapnoea index (AHI) in terms of time spent asleep, excluding intervening periods of wakefulness, and thus provides a more precise assessment of sleep apnoea severity. Although APAP devices can diagnose severe OSAS effectively, their utility in the diagnosis of milder disease remains questionable. The overall cost-benefit of diagnostic pathways involving APAP devices remains unclear as subsequent PSG may still be required in patients with initial non diagnostic APAP studies.

Nonetheless, recent studies in patients with a high probability of having OSAS have produced encouraging results. Mulgrew *et al*[39] in a single-centre controlled study utilised a clinical algorithm incorporating overnight oximetry in the home to identify patients who had a high probability of moderate to severe OSAS, and randomized them to receive either ambulatory titration of CPAP at home without a diagnostic PSG using the AutoSet Spirit machine for 1 wk or to diagnostic PSG followed by titration of CPAP by PSG in the sleep laboratory[39]. They concluded that auto-titrating CPAP therapy can be initiated without additional PSG in patients predicted to have a high probability of OSAS, based on similar measures of patient satisfaction, adherence to CPAP therapy, and CPAP pressures after 3 months in each group. Berry *et al*[40] have also reported similar adherence and clinical outcomes with portable monitoring and auto-titration compared to PSG. Further studies are required to clarify which subgroups of patients suspected of having OSAS may be suitable for diagnosis using APAP alone.

Use of APAP to determine an effective continuous positive airway pressure in patients with OSAS

A full-night, attended PSG performed in the laboratory is the preferred method of CPAP titration prior to the initiation of home positive pressure therapy[41]. Although this approach is regarded as the comparison standard on an *a priori* basis and that other approaches are not superior, it is not the same as proving

full-night PSG is a quality gold standard[42]. Reserving a full night in the laboratory for the initiation of positive pressure therapy allows the patient to be educated prior to the study regarding their diagnosis of the OSAS and the potential benefits of treatment with a positive pressure device. However, this method is costly, time-consuming and adds to the ever-increasing pressures on modern sleep laboratories.

When APAP devices are used for long-term OSAS therapy, treatment initiation is greatly simplified as determination of a single pressure is no longer required and repeat titration during long-term follow up is also made redundant. However, APAP devices have also been utilized over shorter time periods to determine an effective pressure for continued long-term therapy with conventional CPAP. Titration with an APAP device may be performed on a single night in an attended setting, reducing the workload and time of the technician compared to conventional titration. Titration with APAP may also be performed in the unattended home setting over one or several nights, eliminating the need for a second study but also perhaps removing the benefits of in-laboratory education during titration.

Most studies examining the role of APAP in CPAP initiation have used patients with a prior diagnosis of OSAS on PSG. In general, the pressures derived from APAP titration were similar to pressures derived from conventional CPAP initiation with PSG monitoring[38]. High mask leak may, however, impact on the ability to perform auto-titration[43]. Following long-term CPAP prescription of the pressure derived from auto-titration, similar improvements in AHI, subjective sleepiness, sleep architecture and long-term compliance have been reported compared to treatment following conventional titration[25,44,45]. A reduction in cost and the time from diagnosis to final adjustment of CPAP pressure have also been reported[46].

Use of APAP for the treatment of OSAS

A large number of studies have examined the role of APAP devices for the therapy of OSAS[46-56]. Most studies have used largely male populations with moderate-severe or severe OSAS (who may or may not have been CPAP naïve), free of significant co-morbidity and have varied in terms of the study design, duration, APAP devices used and clinical outcomes measured.

In general, the mean treatment pressure with APAP is lower than that delivered by conventional CPAP[38]. Improvements in other polysomnographic variables, measures of sleep propensity, and quality of life scores are largely similar between APAP and conventional CPAP[32].

Overall compliance is comparable between APAP and CPAP, although some studies have shown superior compliance with APAP[51,57-59]. Interestingly, Patruno and colleagues[60] demonstrated that despite showing similar improvements in polysomnographic variables and patient symptoms to conventional CPAP, APAP therapy did not, however, improve cardiovascular risk factors. Further studies are required to establish the effect of APAP on long-term cardiovascular outcomes in treated OSAS patients.

The current AASM practice parameters state that "certain APAP devices may be initiated and used in the self-adjusting mode for unattended treatment of patients with moderate to severe OSA without significant comorbidities[32,33]." Patients being treated either with CPAP on the basis of an APAP titration or with APAP therapy long-term, should have close clinical monitoring to determine treatment efficacy and safety, especially in the initial treatment period[32]. Unresolved clinical symptoms on APAP therapy should prompt a re-evaluation ± a standard in-laboratory CPAP titration with concomitant PSG[32].

Comparison of APAP devices

Although different APAP technologies utilize varying algorithms, to date a limited number of studies have directly compared commercially available APAP devices. Shi *et al*[61] compared a flow-based APAP device with a vibration based device during the first night of OSAS therapy under PSG evaluation. The flow-based device was superior in preventing respiratory events[61]. Senn *et al*[56] assessed 29 CPAP-naive patients with OSAS and compared fixed-pressure CPAP and two APAP technologies, each for 1 month, in a cross-over design. No significant differences between the two APAP devices in terms of symptoms, AHI, mean applied pressure or compliance were found. At the end of the trial, 72 per cent of patients had no preference for either APAP or CPAP, with four (14%) choosing APAP and four CPAP. Nolan *et al*[31] compared three different devices (Autoset Spirit, Breas PV 10i and RemStar Auto) in 27 patients already established on CPAP therapy, with each patient randomized to each APAP device for 4 wk in a crossover trial. All 3 APAP devices utilize flow signal in the determination of the applied pressure. Significant differences were noted in the mean pressure delivered, patient compliance, sleep quality and side effects.

The differences between various APAP devices are acknowledged in the current AASM practice parameters[32]. They outline that only "certain" APAP devices may be appropriate for CPAP titration and long-term OSAS therapy. Further studies are required to compare APAP devices in varying patient cohorts, with particular attention to cost-effectiveness and their effects on cardiovascular outcomes.

C-Flex

C-Flex is an advanced technological option to CPAP therapy in which the positive airway pressure is reduced in the initial phase of expiration on a breath-by-breath basis in proportion to the patient's expiratory flow rate. The first such device was developed by Respironics (C-Flex™; Respironics; Murraysville, PA, USA) and has three comfort levels, allowing differential levels of flexible pressure. The maximum pressure drop is approximately 3cm H_20. ResMed (Sydney; Australia) have developed a similar technology to C-Flex termed expiratory pressure relief (EPR). Optimal pneumatic splinting of the upper airway is maintained toward the end of exhalation when collapse is most likely, thereby delivering effective therapy[62]. It is hypothesised that C-Flex may improve treatment adherence and clinical outcomes by increasing comfort during exhalation[63].

A number of studies have compared C-Flex to conventional CPAP. In a non randomized study, Aloia *et al*[63] demonstrated an average of 1.7 h / night greater usage in the C-Flex treated group compared to CPAP ($P<0.01$). In a randomized, single-blinded study Dolan *et al*[64] showed greater mask comfort on visual analog scales with C-Flex, and improvements in pressure requirements, overall compliance and subjective sleepiness comparable to CPAP therapy. In a randomised control trial by Marshall *et al*[65], initial compliance was greater with C-Flex than CPAP in severe OSAS patients, but CPAP provided a greater improvement in subjective sleep propensity as measured by the Epworth Sleepiness Score (ESS). Other studies comparing C-Flex to CPAP used cross-over designs, in which participants served as their own control, did not demonstrate differential adherence rates. These studies did, however, show that C-Flex improved respiratory indices of OSAS and sleepiness, and that measures of treatment comfort and satisfaction were higher than with CPAP[66-68].

Studies to date on the use of C-Flex have focussed mainly on patients with severe OSAS, the subset of OSAS patient in which CPAP compliance is greatest[69]. Further studies are required to assess the role of C-Flex in milder disease, where compliance rates are lower and the impact of periods of lower positive airway pressure during exhalation may have a greater influence on patient comfort and adherence to therapy. Patients requiring a CPAP pressure greater than 9 cm H_2O also require further studies as C-Flex may improve compliance in this cohort where some individuals may be intolerant of the higher pressures required[67].

A-Flex

A-Flex is a further modification of C-Flex technology by Respironics. During the expiratory phase of the respiratory cycle, A-Flex works in exactly the same way as C-Flex. However, A-Flex also softens the pressure transition from inhalation to exhalation by increasing the pressure delivered more gradually to better mirror the normal breathing rhythm of the CPAP user. A-Flex also helps to prevent the CPAP machine from delivering a pressure that is too high. Studies are required to validate the role of A-Flex devices in the treatment of OSAS.

Summary

Huge progress has occurred in the treatment of OSAS with positive airway pressure over the past 30 years. CPAP has become the mainstay therapy in OSAS but long-term compliance with CPAP continuous to be sub-optimal. Newer technologies such as APAP show promise as alternative options in the diagnosis and long-term treatment of OSAS, as well as harbouring potential to complement the older modalities of PSG and conventional CPAP in the titration of positive airway pressure therapy. However, APAP devices are significantly more expensive than standard CPAP devices. Also, the long-term benefits of APAP therapy, in particular with regard to cardiovascular outcomes, are yet to be established. Furthermore, there is scant evidence to support roles for even newer modalities such as C-Flex and A-Flex. Until more data become available, standard CPAP therapy should continue as the mainstay of OSAS management.

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