REVIEW ARTICLE

Current status of autotitrating continuous positive airway pressure: a review

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Abstract

The prevalence of obstructive sleep apnea (OSA) is increasing requiring easier access to large-scale screening and treatment of general population. Autotitrating Positive Airway Pressure (APAP) devices change effective pressure in a feedback circuit based on airflow, pressure changes, or airway resistance changes. This aids in pressure titration process throughout the sleep period. In patients with moderate to severe OSA without co-morbid conditions APAP and Continuous Airway Pressure (CPAP) are similar in affecting change in Apnea hypopnea index, Arousal index, and Sleep efficiency, Time in REM sleep, Quality of life, and adverse events. According to some studies, there has not been a significant difference in blood pressure changes between the APAP and CPAP groups. Current recommendations are to avoid APAP in patients with clinically significant co-morbid conditions including congestive heart failure, severe COPD, central sleep apnea, asthma and other obstructive pulmonary disorders or obesity hypoventilation syndrome and neuromuscular disorders. Further recommendation is to avoid using APAP for the diagnosis of OSA. Careful patient selection, monitoring of APAP data and proper mask fitting and leak control are essential to the success of APAP therapy. This article reviews the current scientific literature and emphasizes the need for more research before APAP can become the most efficacious mode of OSA treatment.

Obstructive sleep apnea (OSA) prevalence is rising owing to many factors. Among these, obesity epidemic is considered a major confounder. Parallel with this increase in OSA, rapidly building public health and public safety burden drives the need for more widespread screening of the at-risk populations. Over the years, a gradual shift favoring "out of center testing" (OCST), popularly known as home sleep test (HST), portable monitoring (PM), and other names, has occurred. Autotitrating continuous positive airway pressure (APAP) was introduced in 1990, mainly for screening patients for nasal continuous positive airway pressure (CPAP) and for those patients whose health prevented visit to sleep laboratory for testing and CPAP titration. The combination of OCST and APAP use has literally eliminated the need for sleep laboratory from the management of OSA in many patients. The versatile technological design of APAP machine offers a wide range of pressures that responds to patient's variable breathing patterns and behaviors. The ability to track and monitor the results from these machines makes APAP a reasonable choice in properly selected patients.

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Role of APAP Machine in Diagnosing Obstructive Sleep Apnea

The current American Academy of Sleep Medicine (AASM) Practice Parameter update from 2007 for APAP does not recommend the use of AutoPAP in diagnosing OSA[1]. However, APAP can be used in a diagnostic mode (nonreactive to events) to aid in diagnosing OSA. Although similar to HST, it can be done in the familiar environment of patient's own home and a diagnostic report can be generated, there is a paucity of clinical evidence to support this type of testing to establish the diagnosis of OSA. Compared with FDA-approved HST machines, APAP machine may not be suitable for diagnosis, but it is utilized to titrate positive pressure to eliminate obstructive events. A study by Trikalinos et al.[2] suggested a lack of enough data to indicate that types 2-4 portable monitor studies can accurately predict apnea-hypopnea index (AHI) for the diagnosis of OSA with a high likelihood ratio or low likelihood ratio.

Rodenstein[3] raised a concern that APAP devices reacting to snoring and flow limitation without pathological content would lead to overtreatment of what may not be pathology. Because home studies have no observer to determine body position, body position-dependent obstructive breathing abnormalities would not be apparent. The use of APAP for titration may produce unacceptable data that need to be repeated with an in-laboratory polysomnography (PSG). For example, in a multisite randomized-controlled trial (RCT) conducted by Rosen et al.,[4] in the home autotitration, 71% showed technically acceptable titration data on first attempt and 77% on the second attempt with overall 90% having an acceptable autotitration on either first or second attempt.

Adherence Patterns of APAP versus CPAP

It has been recommended that CPAP should be used at least 4 h a night for at least 70% of the treatment period to yield benefit in reduction of AHI and reduction in daytime sleepiness[5-7]. Although positive airway pressure machines are now quieter, improved face and nasal masks have been designed, and algorithms for pressure delivery have been modified, compliance with treatment is still a hurdle for many patients. In a Cochrane collaborative review of various modalities of positive airway pressure in adults with OSA by Smith and Lasserson[8], when participants were asked for their preference, APAP was preferred over CPAP. A statistically significant difference in machine usage of 0.21 (0.08-0.35) h/night was observed in favor of APAP.

However, in a meta-analysis by Ayas et al[9]., adherence to APAP therapy was not significantly greater than with CPAP (pooled estimate of APAP-CPAP adherence= 0.20 [-0.16, 0.57] h/night, $P = 0.28$). In the RCTs chosen for meta-analysis by Ip et al[10]., 20 trials suggested that there were no statistically significant differences in device usage between APAP and CPAP and four reported a significant increase in the use of APAP compared with CPAP. Upon an analysis of the data, a statistically significant difference of 11 min per night favoring APAP (difference= 0.18 h; 95% CI, 0.05-0.31 min; $P = 0.006$) was noted.

An APAP adherence study by Sampaio et al. found that older participants (median age, 57.5 years) and those with a significantly higher AHI (median = 51) were optimally adherent to therapy. In addition, significant adherence factors in the first 3 months of APAP usage were the expectations of outcomes and spiritual support. Other issues showing an effect on compliance included leakage of air from masks, self-efficacy, and the ability to acquire (personally and via family mobilization) and accept support[11].

In a short-term RCT by Bastos et al., they assessed if both AHI and compliance would change with high- and low-pressure range APAPs (high-pressure range, 4-15 mm Hg, $n = 25$; and low-pressure range, 8-12 mm Hg, $n = 28$). After 3 months of APAP treatment, no differences was noted in air leakage or residual AHI; however, the high-pressure group showed poor adherence than that of the low-pressure group (median, 69.5% [44-96%] vs. 96% [83.5-98%])[12].

Effectiveness of APAP in Decreasing Residual AHI and Other Parameters

Making an educated appraisal of APAP treatment is difficult, as different APAP devices monitor and respond to autotitrate based on different parameters. However, outcomes are measured in the same way that all the positive airway pressure devices are compared: the effect on AHI, Epworth Sleepiness Scale score, and mean pressure[13]. According to the 2008 Clinical Guidelines for the Manual Titration of Positive Airway Pressure in Patients with Obstructive Sleep Apnea, an optimal titration decreases RDI less than 5 for at least 15-min duration and should include supine rapid eye movement

(REM) sleep at the selected pressure that is not constantly interrupted by spontaneous arousals or awakenings[14].

In a 2003 meta-analysis by Ayas et al. (9 RCTs, n = 282 patients), APAP showed no significant benefit over CPAP based on device utilization, AHI, and Epworth Sleepiness Scale (pooled APAP-CPAP posttreatment AHI = -0.20 events/h, 95% CI [-0.74, 0.35], and Epworth Sleepiness Scale = -0.56, 95%CI [-1.4, 0.3]). However, the mean pressure was lower in the APAP groups (-2.2 mm Hg) than that in the CPAP groups[9].

In 2011, the Canadian Thoracic Society made the guideline statement that there is no difference in the degree of residual sleep apnea on CPAP between patients managed using PSG versus ambulatory strategies using PM and APAP[15].

A meta-analysis by Ip et al. in 2012 revealed a nonsignificant difference between APAP and CPAP of 0.25 events/h (95% CI, -0.16 to 0.66 events/h; P = 0.23). A decrease in the Epworth Sleepiness Scale of 18 trials for meta-analysis yielded a statistically significant difference between the APAP and the CPAP of -0.48, favoring the APAP treatment (95% CI, -0.81 to -0.15; P = 0.005)[10].

Effect of APAP on Sleep Structure and Insomnia

There is strong support for APAP therapy improving sleep quality as defined as an arousal index of less than or equal to 20 events/h or an increase in either slow-wave or REM sleep or both. In 2001, Berry et al[16]. found four clinical series, one nonrandomized control trial, and 11 RCTs, which met the previous criteria for sleep quality improvement with treatment via an APAP device[16].

The goal of positive airway pressure therapies is to not only reduce the number of obstructive events but also improve the overall quality of sleep structure by increasing the amount of slow-wave sleep. Restorative slow-wave sleep (stage N3) is characterized by high-voltage; synchronized EEG waveforms[17]. Decrease in stage N3 sleep is known to cause substantial daytime sleepiness[18]. Two RCTs determined that APAP treatment increased the levels of slow-wave sleep significantly greater than CPAP. The study by Konermann et al[19]. reported that slow-wave sleep significantly (P < 0.01) increased from 11.4 ± 10.4% to posttest level of 17.6 ± 18.4% on CPAP versus from 13.2 ± 12.2% to 27.2 ± 16.5% on APAP. A study by Scharf et al[20]. found 16.1 ± 22.7 min of slow-wave sleep on CPAP and 32.6 ± 27.4 min on APAP (P < 0.05).

APAP devices may cause microarousals and complete arousals because there are times when a higher pressure must be used to prevent apneic events. Microarousals are brief awakenings ranging from 1.5 to 3 s in duration[21]. In a study of 30 patients with moderate to severe OSA being treated with APAP, Fuchs et al. determined that the overall frequency of microarousals was low, and in most of the study participants, the relative amount of pressure-associated microarousals was not significant. However, microarousals did increase with increasing titrated pressure, but the majority of microarousals (82.5%) were not preceded by a significant change in pressure, 10.6% were associated with a significant prior increase, and 6.9% with a significant prior decrease in pressure[22].

In a prospective study of 80 patients on APAP therapy (39 with insomnia) diagnosed with sleep apnea, Nguyên et al[23]., reported that the insomnia severity index significantly decreased over the 24 months of the study (13.7 ± 5.7 versus 8.2 ± 6.3 from month 0 to month 24, P = 0.0001, mean decrease of 13.5 ± 2.9 as a whole group).

There are mixed answers to this question; there are studies determining that APAP increases stage N3 sleep, and then, other studies show that APAP increases in microarousals and insomnia severity index. The clinical significance may be interpreted as a need for review of stored data in patient's device to be compared with subjective benefit to the patient. Follow-up in-laboratory PSG and titration may still be advisable in uncertain cases.

Effect of APAP on Cardiovascular Risk factors

The oxygen desaturations leading to hypoxemic stress occur repetitively in patients with OSA and drive the renin-angiotensin-aldosterone system to trigger increases in systemic blood pressure. Hypercapnia and hypoxia lead to pulmonary vasoconstriction and chemoreflex-mediated increases in sympathetic activity. This, in turn, promotes the peripheral vasoconstriction with further increases in blood pressure. Arousals from sleep cause sustained daytime sympathetic activation, increase in blood pressure, and elevation of heart rate. Apneic

periods and hypoxia are related to increased endothelial dysfunction, decreased nitrous oxide, and increased reactive oxygen species, which cause inflammation and damage to blood vessels. Hypoxic stress places further demands on the myocardium similar to ischemic insults[24]. Cardiac arrhythmias are common in patients with OSA. In a study by Mehra et al[25]., patients classified as having a severely high AHI demonstrated a 2-4-fold increased risk of nocturnal arrhythmias such as atrial fibrillation and nonsustained ventricular tachycardia[25].

There are many studies that support that CPAP treatment is effective in treating OSA and, subsequently, decreases cardiovascular risk via reduction in sympathetic drive, decreases blood pressure, improves oxygen saturation, and decreases markers of endothelial inflammation[26]. Aldosterone and angiotensin II have been demonstrated to decrease with CPAP treatment for OSA[27]. The major finding by a retrospective study by Patruno et al. was that APAP treatment was not as effective as CPAP in decreasing sympathetic modulation during sleep in participants with OSA. In this study, they observed a significant reduction in systolic blood pressure (SBP) (144 ± 10 to 132 ± 8 mm Hg; $P < 0.001$) and diastolic blood pressure (DBP) (88 ± 4 to 79 ± 6 mm Hg; $P < 0.001$) in the CPAP group but not in the APAP group (SBP: 142 ± 12 to 136 ± 6 mm Hg; DBP: 87.5 ± 4 to 86 ± 4 mm Hg)[26].

In a small study comparing the pre- and posttreatment blood pressures in both APAP and CPAP treatment by Marrone et al., after APAP treatment, SBP decreased during sleep ($P < 0.05$) and DBP decreased during both the awake periods ($P < 0.05$) and the sleep ($P < 0.02$). In addition, in the APAP treatment group, heart rate decreased during the study during both the awake periods (from 87.8 ± 9.4 to 82.2 ± 9.4 beats/min) and the sleep (from 76.4 ± 9.7 to 65.5 ± 5.9 beats/min). Similar changes were observed in subjects receiving CPAP (wake DBP: from 81.1 ± 6.1 to 76.6 ± 5.0 mm Hg; sleep DBP: from 70.0 ± 5.3 to 63.4 ± 9.4 mm Hg; sleep SBP: from 114.5 ± 4.7 to 106.5 ± 9.6 mmHg), in addition to a decrease in heart rate during sleep (from 74.3 ± 11.1 to 65.1 ± 9.1 beats/min). DBP depends partly on arteriolar tone, influenced by sympathetic activity, which is high in patients with OSA during wakefulness and sleep. This suggests that both APAP and CPAP treatments may effectively reduce sympathetic activity and, consequently, reduce blood pressure[28]. On the other hand, a larger RCT study by Pepin et al[29]. suggested that CPAP was better at reducing blood pressure than APAP. From baseline to 4 months, 24-h DBP decreased by 1.7 (3.9/0.5) mm Hg in the CPAP group and by 0.5 (-2.3/1.3) mm Hg in the APAP group [difference between the groups, -1.4 [-2.7/-0.01] mm Hg; $P = 0.0477$). A meta-analysis on the reduction of blood pressure using APAP versus CPAP would be helpful in sorting out whether CPAP has more effect than APAP.

There are many studies focusing on other aspects of cardiovascular function and APAP treatment. In patients with both OSA and congestive heart failure, a randomized double-blinded controlled study by Smith et al[30]. found that APAP improved daytime sleepiness but not other measures of CHF severity. OSA may be an underappreciated modifiable risk factor for both stroke and TIA[31]. The use of APAP as poststroke treatment was explored in a study by Bravata et al. Stroke patients were randomized to the intervention group that received 2 nights of APAP, and those with evidence of sleep apnea received APAP for 30 days, after which they did a PSG. Control patients received PSG at baseline and after 30 days. Change in the stroke severity was assessed comparing the NIH Stroke Scale (NIHSS) at baseline versus at 30 days. The intervention and control groups showed similar baseline stroke severity (both the median NIHSS, 3.0). Patients with APAP intervention revealed greater improvements in NIHSS (-3.0) than control patients (-1.0, $P = 0.03$), concluding that APAP appears to improve neurological recovery[32].

Effect of APAP on Metabolism and Biomarkers of Inflammation

There have been numerous studies on the effects of CPAP treatment on biomarkers of inflammation in patients with OSA. However, at the time of writing, there were limited studies relating APAP treatment to the levels of inflammatory markers.

A study by Mysliwiec et al[33]. suggested that insulin-like growth factor (IGF)-1 may serve as a possible biomarker for the efficacy of APAP therapy ($n = 58$ male subjects, prospective observational). Patients adherent to APAP showed concentrations of IGF-1 that were significantly higher (128 ± 59.5 ng/mL) compared with nonadherent participants (86.0 ± 47.4 ng/mL; $P < 0.01$).

Increases in IGF-1 were significantly related with decreases in AHI (Spearman's rho = -0.409, $P = 0.015$). C-reactive protein (CRP) concentrations did not differ

between baseline and follow-up measurements in either group. Decreased growth hormone secretion is related to decrease IGF-1 levels. Growth hormone and IGF-1 decreases are associated with an increase of the AHI and decrease in the interval of sleep[34,35].

The previously mentioned study by Patruno et al[26]. also made note that CRP plasma levels were similarly reduced in both the CPAP group (0.8 ± 0.3 to 0.46 ± 0.38 mg/dL; $P < 0.001$) and the APAP group (0.6 ± 0.2 to 0.47 ± 0.4 mg/dL; $P < 0.001$)[26].

Drummond et al. found no significant decrease in CRP and interleukin-6 with APAP treatment (9 days and 6 months; CRP: $P = 0.720$ and $P = 0.387$, respectively; IL-6: $P = 0.266$ and $P = 0.238$, respectively)[36].

It would be interesting to see further studies relating APAP treatment to the levels of markers of vascular inflammation and oxidative stress, especially tumor necrosis factor alpha, VEGF, and 8-isoprostane.

Conclusion

APAP treatment of OSA requires further scrutiny. There are limited data on the effects of the ability of APAP to decrease markers of inflammation and suggestions that APAP is not as effective at decreasing sympathetic activation. Further study is needed to determine the adequacy of the algorithm of pressure response in determining the effective pressure level during home titration using APAP[37]. Each device has its own internal algorithm for determining the required pressure, and the high and low pressures differ depending on the proprietary algorithm. Over time, even APAP devices require some adjustment, and follow-up is required to monitor for the safe and effective usage and residual AHI. However, some devices can now be adjusted remotely[1]. APAP appears to reduce AHI equally and CPAP in short-term studies; nevertheless, longer-term studies are warranted to re-affirm this benefit.

Whether APAP should be used for long-term treatment of OSA or not at this time is a clinical decision. Patients who have congestive heart failure, severe chronic obstructive pulmonary disease, central sleep apnea, asthma and other obstructive pulmonary disorders, or obesity hypoventilation syndrome are not suitable candidates for APAP[1,16,38-40]. The technology is evolving quickly to produce devices that are generally well tolerated and effective for many phenotypes of patients with OSA. Home testing and home APAP titration may help increased access to diagnosis and treatment over a relatively shorter period of time while reducing the health-care costs.

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