Published in final edited form as:
Sleep Med Clin. 2010 September 1; 5(3): 361–368. doi:10.1016/j.jsmc.2010.05.010.

APAP and Alternative Titration Methods

Omer Ahmed[1] and **Sairam Parthasarathy, MD**[2,3]

[1] Fellow, Pulmonary and Critical Care Medicine, Department of Medicine, University of Arizona, Tucson, AZ

[2] Chief of Research, Southern Arizona Veterans Administration Healthcare System, University of Arizona, Tucson, AZ

[3] Associate Professor of Medicine, Department of Medicine, University of Arizona, Tucson, AZ

Abstract

Purpose of review—Positive airway pressure therapy (PAP) is commonly prescribed treatment for obstructive sleep apnea (OSA). Traditionally, the determination of the optimal pressure for treatment of sleep-disordered breathing was made by manual titration of the device by a sleep technician in attendance during polysomnography. However, the advent of alternative methods for determination of optimal PAP – such as auto-titrating PAP (APAP) – has seen tremendous growth over the past decade. The purpose of this review is to improve our understanding of the currently available alternative methods for titration of PAP in patients with sleep-disordered breathing (SDB) with special emphasis on obstructive sleep apnea.

Recent Findings—Recent prospective-randomized studies of alternative methods of titration suggest that pressure determinations made by such devices are comparable to traditional manual titrations made in the sleep laboratory. Obstacles to the adoption of such alternative modes of titration into day-to-day practice may be attributable to issues surrounding appropriate patient selection, differences between devices, re-imbursement policies of third party payors, consensus amongst sleep experts, and individual physicians' practice patterns and volumes. While newer generations and types of auto-titrating PAP devices are entering the sleep field constantly, providers' knowledge and time availability remain limiting factors.

Summary—There is tremendous growth in the technology and scientific evidence in support of alternative modes of PAP titration for sleep-disordered breathing, but barriers to implementation remain.

Keywords

obstructive sleep apnea; continuous positive airway pressure; adherence; adult; pediatric; compliance; sleep apnea; artificial respiration; titration; automatic

Corresponding Author: Sairam Parthasarathy, MD, Chief of Research, Southern Arizona VA Health Care System, Associate Professor of Medicine, University of Arizona, 3601 S. Sixth Avenue, Mail Stop 0-151, Tucson, AZ 85723, Ph: 520-629-1824, Fax: 520-629-1801, spartha@arc.arizona.edu.
Co-author: Omer Ahmed, MD, Fellow, University of Arizona, 1501 N. Campbell, Ave., Rm. 2342B, P. O. Box 245030, Tucson, AZ 85724, Ph: 520-626-6114, Fax: 520-629-1801, oahmed.md@gmail.com

Introduction and Historical Perspective

Ever since the first report of continuous positive airway pressure (CPAP) for treatment of obstructive sleep apnea (OSA) was made in 1981, the methodologies and end-points for titration of the CPAP level was quickly brought to the forefront (1). Publications on the alternatives to manual in-laboratory polysomnography (PSG) based titrations of PAP did not occur until a decade later (2–4). Intelligent devices with in-built microprocessors for detection and treatment of events of SDB have gone by different names ranging from self-adjusting, to automatic, auto-adjusting, smart CPAP, and auto-titrating PAP (APAP). The purpose of APAP devices was varied and included the replacement of in-laboratory manual titration, reducing mean pressures to achieve better adherence, and adapting CPAP levels to changes in severity of OSA in response to changes in weight, sleep state, body position, and alcohol ingestion. Today the purpose of automation has expanded towards detecting and ameliorating central apneas and hypoventilation. The purpose of this review is to provide an up to date synthesis of APAP technology, scientific evidence in support of APAP use, and issues surrounding the regulation, reimbursement and health services aspects of APAP therapy.

Technology

The functioning of APAP devices can be broken down into three components: sensing of events of SDB (*sensors*), automated computing and analysis of the sensed signals (*analysis)*, and hierarchal set of algorithms that will determine the action taken by the APAP device in response to the conditions exposed (*effectors)*.

In the older generation of APAP devices, the *sensors* were simplistic and measured only the pressure inflections (vibrations) of a certain frequency and amplitude that were caused by snoring. Subsequently, the next generation of APAP devices became more sophisticated and were able to sense flow-based changes such as apnea, hypopnea, or inspiratory flow limitation based upon the inspiratory flow contour (i.e., flattening of the inspiratory flow waveform). More recently, devices have developed to differentiate central from obstructive apneas (using forced oscillation technique or rapid injection of air), identify Cheyne-Stokes respiration (by breath-by-breath changes in peak flow), identify hypoventilation (by measuring tidal volume or minute ventilation 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)(5). Such signals are computed and analyzed instantaneously by a built-in microprocessor with preset hierarchical set of algorithms that will determine the rate and magnitude of pressure response.

APAP devices may increase the pressure in response to events such as apneas and 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, i.e., 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)(6). 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 to not only increase bit also decrease the pressure on certain occasions. The APAP device may reduce the pressure when the inspiratory flow curve has the convexity facing upwards or if there have been no events of SDB detected over a certain period. Such algorithms are proprietary and a provider should probably be well informed regarding their characteristics before prescribing such an APAP device (7).

The *effector* arm of the APAP device has undergone radical changes as well. Newer generation devices can not only increase the CPAP level, but can also increase the inspiratory positive

airway pressure (IPAP) alone in order to ameliorate obstructive events (Auto Bi-level PAP), correct hypoventilation (averaged volume assured pressure support [AVAPS], or autoVPAP) or combat central apneas in patients with complex sleep apnea or CPAP-emergent central apneas (Servo-Ventilation)(8–11). Devices may also introduce a back-up rate to prevent central apneas and although in general they are not referred to as APAP devices, they function using similar principles and can be judged as the latest generation of APAP devices (10,11).

Scientific evidence

The scientific evidence governing auto-titrating and other alternative methods for titrating PAP devices continue to evolve. Both bench and clinical studies need to be considered in assessing such auto-titrating methods. However, while the bench studies provide valuable information regarding the performance of APAP devices by controlling their exposure to artificially simulated apneas and hypopneas, only clinical trials with measured benefits to patient-outcomes should guide practice.

Bench studies

Numerous bench studies have been performed comparing the devices made by different manufacturers across different generations of devices (6,12–15). Such studies have consistently shown that for a given set of events characterizing SDB, the responses of devices from different manufacturers are quite different. One particular study demonstrated the scatter in pressure response of four older-generation APAP devices to be as wide as 10 cm H_2O (6). Such changes may be attributable to the APAP devices' ability to sense the event or the pre-programmed algorithms that determine the rate of pressure change and magnitude of step change in pressure(7). Moreover, bench studies have shown that air-leak deleteriously affected the performance of APAP devices (6,13,15), and that some devices were less likely to be influenced by air-leak than others (6). In addition, humidifiers may act as a capacitor and muffle some of the 'snoring' pressure waveforms before they reach the sensors in the APAP device. Predictably, in at least one bench study, humidifiers resulted in a small reduction (2 cm H_2O) in pressure response over a 5-minute run (6). Despite such bench studies, there are currently no published clinical studies that have identified the *clinical implications* of the effects of air-leak or humidifiers on APAP device performance. Such clinical studies are needed rather than to extrapolate findings from bench studies to the clinical realm. Limitations of bench studies include the brief duration of simulations, highly controlled conditions, apnea simulators that do not respond to changes in pressure administered by the APAP device (referred to as "open loop" system), or failure to account for patient co-morbidities that may influence pressure response (nasal congestion, palatal surgery, or morbid obesity).

Clinical effectiveness

A large body of clinical trials aimed at assessing the efficacy of APAP and other alternative methods to titrate APAP devices have accumulated over the past decade. This review will focus primarily on randomized controlled trials (RCT).

Dating back to the first publications of randomized controlled prospective trials of APAP in 1996, until now, most if not all RCTs have demonstrated that APAP devices can be used to determine the 'fixed' treatment pressure that is comparable to the gold standard (attended manually titrated CPAP during polysomnography [PSG])(16,17). Subsequently, using older generation APAP devices, investigators have demonstrated that the "fixed" CPAP pressure determined by APAP therapy can either be the same, greater, or less than that derived from attended PSG (17–20). Such a simplistic comparison, however, should probably not be made considering that; the gold standard itself suffers from inherent limitations – cost, inconvenience of electrode placements, laboratory versus home environment, and limited "one-night"

sampling. A better benchmark would be to consider patient outcomes such as patient preference, patient comfort, treatment adherence, and improvements in other clinical end-points (sleepiness, health-related quality of life [HR-QOL], cardiovascular and neurocognitive measures). Most of these RCTs recruited CPAP-naïve patients with moderate to severe OSA and avoided co-morbid conditions that would deleteriously affect performance of APAP devices (21). Some of the exclusionary criteria were nasal obstruction, palatal surgery, and morbid obesity with hypoventilation, central sleep apnea, co-existent heart failure or chronic obstructive pulmonary disease (COPD).

In a large European study, Masa and colleagues randomized 360 CPAP-naïve patients to either APAP, CPAP titration during full night PSG, or a prediction formula-based CPAP level in a multi-center RCT (22). In this study, APAP was initiated at home after the patient received instructions and mask fitting in an outpatient setting. Over a 3-month period, improvements in subjective sleepiness, disease-specific HR-QOL measures, and 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 HR-QOL measures that were not tailored for assessing patients with SDB, improved to a slightly lesser magnitude in the APAP group when compared to PSG- or formula-based methods for determining treatment CPAP level (effect size ≤ 0.5). Another very recent study identified patients with OSA using either PSG or limited PSG, and then randomized the subjects and crossed them over to receive either APAP or PSG-derived CPAP therapy (23). Patients in the APAP 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 HR-QOL was not different in the two groups. Study limitations included issues surrounding the cross-over 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 APAP therapy (23).

Noseda and colleagues, however, did select and study patients who were more likely to benefit form APAP therapy, namely patients with a high within-night variability in APAP-titrated pressure levels (24). However, they failed to demonstrate any difference in PAP adherence or mean pressure levels when compared to PSG-derived CPAP trial over an 8-week treatment period. Although subjective ratings for sleepiness were better with APAP therapy, such improvements were not clearly explained by group differences in pressure or adherence levels (24). Similarly, Massie and colleagues selected patients requiring a CPAP pressure level of 10 cm H_2O or more, and reported that APAP therapy resulted in greater improvements in HR-QOL and self-reported sleep quality than conventional laboratory PSG-determined fixed CPAP pressure (25). One study, however reported APAP therapy failed to reduce AHI as much as conventional PSG-derived CPAP settings (26). In this study by Patruno and colleagues, blood pressure and insulin resistance improved to a lesser degree in the APAP group when compared to the group receiving conventional PSG-derived CPAP therapy (26). Interestingly, this study had rather lenient exclusion criteria that did not exclude patients with significant co-morbid conditions. Moreover, in a study employing APAP device technology, intensive home support with monthly home visits over a 6-month period of time was more effective in achieving adherence to PAP therapy than the relatively more expensive APAP device technology (27). Considering the expenditure of provider time in issuing APAP, downloading and interpreting the APAP device outputs, and monitoring patients following initiation of APAP therapy, cost-effectiveness analysis of APAP therapy versus conventional treatment methodologies is direly needed in order to justify their use.

Forced oscillation technology (FOT) 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 FOT-based APAP versus laboratory PSG-derived CPAP found that the pressure recommendation between these two methodologies were comparable, and they achieved similar reductions in AHI and self-reported sleepiness over a 6-week period (28).

The use of APAP therapy in patients who have *not* undergone conventional PSG for establishing the diagnosis of OSA has also seen tremendous growth. Berry and colleagues performed a RCT wherein patients underwent portable testing for OSA based upon a tonometry- and actigraphy- based system (29). In 106 patients with daytime sleepiness and a high likelihood of having OSA, administration of APAP versus PSG-derived CPAP did not result in any differences in adherence to PAP therapy, improvement in sleepiness, improvement in HR-QOL, or patient satisfaction levels. 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, this study highlighted the ability of APAP to achieve benefits comparable to PSG-derived CPAP levels when used with home study testing without electroencephalography (29). In another study that did not use PSG, Mulgrew and colleagues have demonstrated that PSG-derived CPAP titration did not confer any advantage over APAP therapy initiated following identification of OSA by sequential application of the Epworth Sleepiness Scale (ESS) score, Sleep Apnea Clinical Score, and overnight oximetry (30). In fact, in this study, patients randomized to APAP group were more adherent to PAP therapy than those in the conventional PSG-derived CPAP pressure group (30). One limitation was the fact that the study was designed as a superiority trial and the need for large studies designed as non-inferiority trials are still needed. Another very recent study has moved further down this aggressive path by using only a Berlin questionnaire to diagnose OSA in a US Veterans population (31). Patients with high likelihood of OSA (n=109) who were awaiting diagnostic PSG were randomized to remain in the conventional pathway or assigned to APAP therapy which was initiated on an outpatient basis. In this study by Drummond and colleagues, patients with two or more positive responses in the Berlin questionnaire, APAP therapy resulted in improvement in self-reported symptoms and disease-specific HR-QOL 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 with 66% of eligible patients being excluded due to the presence of co-morbid conditions such as heart failure and COPD (31).

Nurse-led home-based initiation of APAP therapy in a large non-inferiority trial encompassing 619 subjects – to date the largest published RCT involving APAP therapy – demonstrated equivalence compared to patients treated by sleep physicians using conventional PSG (32). In this study, Antic and colleagues also demonstrated lower costs in the nurse-led group (32). Such large non-inferiority trials need to be replicated in the US for change in practice to occur.

Clinical comparisons between different APAP devices have been made in a randomized controlled manner. In a cross-over study design with three conditions and 1-month period of therapy, Senn and colleagues two different APAP devices and CPAP therapy based on pressure level determined following 2-weeks of APAP therapy (33). Patients received the three treatments in a random manner over three consecutive 1-month periods. All three treatment modalities achieved comparable improvements in symptoms, quality-of-life domains, and AHI. Series and colleagues performed a similar trial with a 10-day washout period between three different APAP devices. Each patient underwent therapy for a one-week home trial. They found that the median pressure value during therapy with one manufacturer's device (5.9 cm H_2O) was significantly lower than that during therapy with the other two devices (7.4 cm H_2O)(34). Such clinical results parallel the bench study findings of the precursor devices from the same manufacturers (6). Such results would suggest that bench study results might indeed be extrapolated to the clinical realm. Despite the inherent limitations of such extrapolation,

such bench testing may be of value considering that devices constantly undergo upgrades and enhancements that outdate, and thereby minimize, the value of comprehensive clinical trial testing (7,35). Interestingly, in a survey of board-certified sleep physicians, only 37% of physicians who prescribed APAP preferred a particular brand (36). Such data may underscore the need incongruence between scientific evidence and day-to-day practice and calls for better dissemination of study findings.

A study (total n=83) comparing PSG-derived CPAP and four different APAP devices administered to patients with severe OSA over a 6-month time period revealed no differences in adherence, clinical symptoms, or HR-QOL (37). Despite differences in the mean CPAP, pressure delivered by the different devices, there clinically no significant differences over the 6-month treatment period. This study, however, was not adequately powered to prove equivalence but raises interesting questions concerning the clinical significance of small differences in therapeutic pressure administered (37).

The comparative effectiveness research (CER) strategic framework calls for generation, synthesis and dissemination of alternate methods to treat and monitor complex medical conditions (such as OSA) requiring complex interventions (such as medical devices in OSA) (38). The development of alternate methods to titrate and treat OSA, or other forms of SDB such as obesity hypoventilation and central sleep apnea are in the spirit of this call. More work on how and where such therapies are being delivered by pragmatic studies analyzing outcomes in patients with complex co-morbid medical conditions subjected to APAP therapy may be needed to increase the reach and universal acceptance of such alternate methods of titration. Specifically, most, if not all of the RCTs, have excluded patients with significant co-morbid conditions that could cause hypoventilation (morbid obesity and COPD) and central apneas (heart failure). Reports from large databases housing patients with such co-morbidities are needed if the field were to advance and be made generalizable to patients in our practice.

Advanced methods of titration

Advanced automation in titration that could tackle central apneas has been developed and is currently marketed. Small RCTs have shown that servo-ventilation made by different manufacturers can successfully detect and treat central apneas (10,11,39,40). Some of these studies have demonstrated improvement in objectively measured sleepiness and urinary measures of catecholamines (40). However, large studies on the effects of such devices on other patient outcomes such as HR-QOL, cardiac function, adherence to PAP therapy have not been published.

During servo-ventilation, the expiratory positive airway pressure is set at a level to 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. Combining APAP and servo-ventilation, with APAP determining the EPAP level automatically, whereas the servo-ventilation controlling periodic breathing and central apneas has been recently reported to be effective in ameliorating SDB (41). RCTs employing such a device are however awaited.

Advanced titration methods for patients with hypoventilation target minute ventilation and tidal volume rather than events of sleep-disordered breathing such as apneas and hypopneas (8,9). While better ventilation and gas exchange have been observed, studies using such devices have failed to demonstrate advantages over conventional bi-level PAP settings with regards to improvements in sleep quality (8,9).

Other titration methods

A small randomized, single-blind, two-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 (42). The prediction formula was derived from readily available parameters – namely, body mass index, neck circumference, and AHI (43). Patients were subsequently encouraged to adjust the pressure as necessary to maximize comfort and perceived efficacy (42). 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 two groups. However, this was a small study. In a much larger afore-mentioned study, Masa and colleagues subjected one-third of the patients to the prediction formula (predicted pressure = (0.16 × BMI) + (0.13 × neck circumference) + (0.04 × AHI) − 5.12 up to a maximum of 9 cm H_2O) and the other two groups were either managed in the conventional laboratory PSG-derived pressure or APAP derived pressure (22). Patients who exceeded a requirement of 9 cm H_2O based upon the formula, were prescribed only 9 cm H_2O and asked to self-adjust the pressure upwards in 1 or 2 cm H_2O 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 APAP, the predicted formula achieved comparable pressure levels when compared to laboratory PSG-derived CPAP levels. There was no difference between all 3 groups with respect to AHI, subjective sleepiness, or PAP adherence levels (22). Other prediction formula exist but have not been studied in a RCT (44).

Regulation, Reimbursement and the Provider

APAP devices, like CPAP devices, are undergoing constant change and evolution. The sophisticated APAP devices of today are a result of multiple incremental changes over many years since the inception of the ‘auto’ concept. This is a natural process that pertains to any device, and is a much different process than drug development. There are advantages and disadvantages to this constant evolution which is done through a 510(k) clearance process (35). The disadvantage to such constant changes is that before a clinical trial of a particular device is completed and published, the device has undergone numerous modifications by the manufacturer. Such changes undermine the relevance of the eventual publication of the clinical trial findings. Whereas, the perfect clinical study following the development of the perfect APAP device will probably never happen, prescribing physicians should pay close attention to changes and characteristics of the APAP devices they prescribe. Changes in device regulation are afoot and may change the landscape of device innovation and afore-mentioned opinions regarding clinical research involving such devices (35).

While APAP devices are generally categorized as low-risk devices by the Food and Drug Administration, their performance in an individual patient may depend on how they are set, where they are set-up, how patients are selected and instructed, and how patients on such therapy are monitored (45). The concern is that physicians in busy practices may be unable to keep up with the changes in technology. Unlike pharmaceutical products, physicians do not receive information regarding post-approval trials, nor do they receive education by a cadre of pharmaceutical representatives. In a 2004 survey of board-certified sleep physicians, only 30% of physicians correctly identified the contra-indications for administration of APAP devices (36). Moreover, thirty percent of sleep physicians never prescribed APAP devices. Physicians who never prescribe APAP devices tended to interpret fewer sleep studies and tended to prescribe fewer PAP devices per month than physicians who prescribed APAP devices suggesting that patient volumes were indicative of physician confidence in prescribing such devices (36). Moreover, 90% of physicians who prescribed auto-PAP devices reported that they reviewed the data downloaded from the device for pressure, leak, and adherence

information. The time spent in interpreting the downloads for leak, appropriate pressure level, and troubleshooting during care delivery in an ambulatory APAP program are, however, not reimbursed for physician time. Future policy changes to reimbursement should consider provider compensation to such care delivery if APAP is envisioned to be embraced by providers.

Conclusion

There has been rapid developments in both the technology and clinical evidence supportive of APAP and other alternate methods of titration. While the results of at least three large non-inferiority trials are earnestly anticipated in this area, the future of APAP and alternative modes of titration in day-to-day practice still rests in the hands of policy makers, regulatory bodies, and expert consensus (35,45,46). Future research needs to move this field ahead from scientific evidence derived from such RCTs to development and dissemination of CER that address the incorporation of such tools in complex medical systems of health care delivery.

Acknowledgments

This work was supported by Grant No. HL095748 from the National Institutes of Health.

Dr. Parthasarathy has received research grant funding between 2006–2007 for $200,000 from Respironics, Inc. Dr. Parthasarathy received support form NIH/NHLBI (HL095748) during the writing of this manuscript. Dr. Ahmed does not have any conflict of interest to disclose.

References

1. Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. Lancet 1981 Apr 18;1(8225):862–5. [PubMed: 6112294]
2. Chediak AD, Lipson E, Demirozu MC, Kiel M. The second generation of nasal continuous positive airway pressure devices. Are they created equal? Sleep 1993 Oct;16(7):662–7. [PubMed: 8290861]
3. Miles LE, Buschek GD, McClintock DP, Miles SC, Narvios LR, Wang YX. Development and application of automatic nasal CPAP calibration procedures for use in the unsupervised home environment. Sleep 1993 Dec;16(8 Suppl):S118–9. [PubMed: 8177998]
4. Berthon-Jones M. Feasibility of a self-setting CPAP machine. Sleep 1993 Dec;16(8 Suppl):S120–1. discussion S1–3. [PubMed: 8177999]
5. Ficker JH, Clarenbach CF, Neukirchner C, Fuchs FS, Wiest GH, Schahin SP, et al. Auto-CPAP therapy based on the forced oscillation technique. Biomed Tech (Berl) 2003 Mar;48(3):68–72. [PubMed: 12701337]
6. Coller D, Stanley D, Parthasarathy S. Effect of air leak on the performance of auto-PAP devices: a bench study. Sleep Breath 2005 Dec;9(4):167–75. [PubMed: 16273421]
7. Brown LK. Autotitrating CPAP: how shall we judge safety and efficacy of a “black box”? Chest 2006 Aug;130(2):312–4. [PubMed: 16899825]
8. Ambrogio C, Lowman X, Kuo M, Malo J, Prasad AR, Parthasarathy S. Sleep and non-invasive ventilation in patients with chronic respiratory insufficiency. Intensive Care Med 2009 Feb;35(2):306–13. [PubMed: 18795255]
9. Storre JH, Seuthe B, Fiechter R, Milioglou S, Dreher M, Sorichter S, et al. Average volume-assured pressure support in obesity hypoventilation: A randomized crossover trial. Chest 2006 Sep;130(3): 815–21. [PubMed: 16963680]
10. Morgenthaler TI, Gay PC, Gordon N, Brown LK. Adaptive servoventilation versus noninvasive positive pressure ventilation for central, mixed, and complex sleep apnea syndromes. Sleep 2007 Apr 1;30(4):468–75. [PubMed: 17520791]
11. Teschler H, Dohring J, Wang YM, Berthon-Jones M. Adaptive pressure support servo-ventilation: a novel treatment for Cheyne-Stokes respiration in heart failure. Am J Respir Crit Care Med 2001 Aug 15;164(4):614–9. [PubMed: 11520725]

12. Lofaso F, Desmarais G, Leroux K, Zalc V, Fodil R, Isabey D, et al. Bench evaluation of flow limitation detection by automated continuous positive airway pressure devices. Chest 2006 Aug;130(2):343–9. [PubMed: 16899831]

13. Farre R, Montserrat JM, Rigau J, Trepat X, Pinto P, Navajas D. Response of automatic continuous positive airway pressure devices to different sleep breathing patterns: a bench study. Am J Respir Crit Care Med 2002 Aug 15;166(4):469–73. [PubMed: 12186822]

14. Hirose M, Honda J, Sato E, Shinbo T, Kokubo K, Ichiwata T, et al. Bench study of auto-CPAP devices using a collapsible upper airway model with upstream resistance. Respir Physiol Neurobiol 2008 Jun 30;162(1):48–54. [PubMed: 18499537]

15. Rigau J, Montserrat JM, Wohrle H, Plattner D, Schwaibold M, Navajas D, et al. Bench model to simulate upper airway obstruction for analyzing automatic continuous positive airway pressure devices. Chest 2006 Aug;130(2):350–61. [PubMed: 16899832]

16. Sharma S, Wali S, Pouliot Z, Peters M, Neufeld H, Kryger M. Treatment of obstructive sleep apnea with a self-titrating continuous positive airway pressure (CPAP) system. Sleep 1996 Jul;19(6):497–501. [PubMed: 8865508]

17. Teschler H, Berthon-Jones M, Thompson AB, Henkel A, Henry J, Konietzko N. Automated continuous positive airway pressure titration for obstructive sleep apnea syndrome. Am J Respir Crit Care Med 1996 Sep;154(3 Pt 1):734–40. [PubMed: 8810613]

18. Lloberes P, Ballester E, Montserrat JM, Botifoll E, Ramirez A, Reolid A, et al. Comparison of manual and automatic CPAP titration in patients with sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med 1996 Dec;154(6 Pt 1):1755–8. [PubMed: 8970366]

19. Teschler H, Wessendorf TE, Farhat AA, Konietzko N, Berthon-Jones M. Two months auto-adjusting versus conventional nCPAP for obstructive sleep apnoea syndrome. Eur Respir J 2000 Jun;15(6):990–5. [PubMed: 10885414]

20. Lloberes P, Rodriguez B, Roca A, Sagales MT, de la Calzada MD, Gimenez S, et al. Comparison of conventional nighttime with automatic or manual daytime CPAP titration in unselected sleep apnea patients: study of the usefulness of daytime titration studies. Respir Med 2004 Jul;98(7):619–25. [PubMed: 15250227]

21. To KW, Chan WC, Choo KL, Lam WK, Wong KK, Hui DS. A randomized cross-over study of auto-continuous positive airway pressure versus fixed-continuous positive airway pressure in patients with obstructive sleep apnoea. Respirology 2008 Jan;13(1):79–86. [PubMed: 18197915]

22. Masa JF, Jimenez A, Duran J, Capote F, Monasterio C, Mayos M, et al. Alternative methods of titrating continuous positive airway pressure: a large multicenter study. Am J Respir Crit Care Med 2004 Dec 1;170(11):1218–24. [PubMed: 15282204]

23. Vennelle M, White S, Riha RL, Mackay TW, Engleman HM, Douglas NJ. Randomized controlled trial of variable-pressure versus fixed-pressure continuous positive airway pressure (CPAP) treatment for patients with obstructive sleep apnea/hypopnea syndrome (OSAHS). Sleep Feb 1;33(2):267–71. [PubMed: 20175411]

24. Noseda A, Kempenaers C, Kerkhofs M, Braun S, Linkowski P, Jann E. Constant vs auto-continuous positive airway pressure in patients with sleep apnea hypopnea syndrome and a high variability in pressure requirement. Chest 2004 Jul;126(1):31–7. [PubMed: 15249439]

25. Massie CA, McArdle N, Hart RW, Schmidt-Nowara WW, Lankford A, Hudgel DW, et al. Comparison between automatic and fixed positive airway pressure therapy in the home. Am J Respir Crit Care Med 2003 Jan 1;167(1):20–3. [PubMed: 12406840]

26. Patruno V, Aiolfi S, Costantino G, Murgia R, Selmi C, Malliani A, et al. Fixed and autoadjusting continuous positive airway pressure treatments are not similar in reducing cardiovascular risk factors in patients with obstructive sleep apnea. Chest 2007 May;131(5):1393–9. [PubMed: 17494789]

27. Damjanovic D, Fluck A, Bremer H, Muller-Quernheim J, Idzko M, Sorichter S. Compliance in sleep apnoea therapy: influence of home care support and pressure mode. Eur Respir J 2009 Apr;33(4):804–11. [PubMed: 19129293]

28. Galetke W, Randerath WJ, Stieglitz S, Laumanns C, Anduleit N, Richter K, et al. Comparison of manual titration and automatic titration based on forced oscillation technique, flow and snoring in obstructive sleep apnea. Sleep Med 2009 Mar;10(3):337–43. [PubMed: 18650127]

29. Berry RB, Hill G, Thompson L, McLaurin V. Portable monitoring and autotitration versus polysomnography for the diagnosis and treatment of sleep apnea. Sleep 2008 Oct 1;31(10):1423–31. [PubMed: 18853940]
30. Mulgrew AT, Fox N, Ayas NT, Ryan CF. Diagnosis and initial management of obstructive sleep apnea without polysomnography: a randomized validation study. Ann Intern Med 2007 Feb 6;146 (3):157–66. [PubMed: 17283346]
31. Drummond F, Doelken P, Ahmed QA, Gilbert GE, Strange C, Herpel L, Frye MD. Empiric Auto-titrating Continuous Positive Airway Pressure in Obstructive Sleep Apnea Suspects. J Clin Sleep Med. 2010
32. Antic NA, Buchan C, Esterman A, Hensley M, Naughton MT, Rowland S, et al. A randomized controlled trial of nurse-led care for symptomatic moderate-severe obstructive sleep apnea. Am J Respir Crit Care Med 2009 Mar 15;179(6):501–8. [PubMed: 19136368]
33. Senn O, Brack T, Matthews F, Russi EW, Bloch KE. Randomized short-term trial of two autoCPAP devices versus fixed continuous positive airway pressure for the treatment of sleep apnea. Am J Respir Crit Care Med 2003 Dec 15;168(12):1506–11. [PubMed: 14525804]
34. Series F, Plante J, Lacasse Y. Reliability of home CPAP titration with different automatic CPAP devices. Respir Res 2008;9:56. [PubMed: 18652688]
35. Garber AM. Modernizing device regulation. N Engl J Med Apr 1;362(13):1161–3. [PubMed: 20335575]
36. Parthasarathy S, Habib M, Quan SF. How are automatic positive airway pressure and related devices prescribed by sleep physicians? A web-based survey. J Clin Sleep Med 2005 Jan 15;1(1):27–34. [PubMed: 17561612]
37. Meurice JC, Cornette A, Philip-Joet F, Pepin JL, Escourrou P, Ingrand P, et al. Evaluation of autoCPAP devices in home treatment of sleep apnea/hypopnea syndrome. Sleep Med 2007 Nov;8 (7–8):695–703. [PubMed: 17638595]
38. VanLare JM, Conway PH, Sox HC. Five next steps for a new national program for comparative-effectiveness research. N Engl J Med Mar 18;362(11):970–3. [PubMed: 20164480]
39. Arzt M, Wensel R, Montalvan S, Schichtl T, Schroll S, Budweiser S, et al. Effects of dynamic bilevel positive airway pressure support on central sleep apnea in men with heart failure. Chest 2008 Jul; 134(1):61–6. [PubMed: 17951617]
40. Pepperell JC, Maskell NA, Jones DR, Langford-Wiley BA, Crosthwaite N, Stradling JR, et al. A randomized controlled trial of adaptive ventilation for Cheyne-Stokes breathing in heart failure. Am J Respir Crit Care Med 2003 Nov 1;168(9):1109–14. [PubMed: 12928310]
41. Randerath WJ, Galetke W, Kenter M, Richter K, Schafer T. Combined adaptive servo-ventilation and automatic positive airway pressure (anticyclic modulated ventilation) in co-existing obstructive and central sleep apnea syndrome and periodic breathing. Sleep Med 2009 Sep;10(8):898–903. [PubMed: 19303811]
42. Fitzpatrick MF, Alloway CE, Wakeford TM, MacLean AW, Munt PW, Day AG. Can patients with obstructive sleep apnea titrate their own continuous positive airway pressure? Am J Respir Crit Care Med 2003 Mar 1;167(5):716–22. [PubMed: 12598214]
43. Hoffstein V, Mateika S. Predicting nasal continuous positive airway pressure. Am J Respir Crit Care Med 1994 Aug;150(2):486–8. [PubMed: 8049834]
44. Loredo JS, Berry C, Nelesen RA, Dimsdale JE. Prediction of continuous positive airway pressure in obstructive sleep apnea. Sleep Breath 2007 Mar;11(1):45–51. [PubMed: 17089145]
45. Morgenthaler TI, Aurora RN, Brown T, Zak R, Alessi C, Boehlecke B, et al. Practice parameters for the use of autotitrating continuous positive airway pressure devices for titrating pressures and treating adult patients with obstructive sleep apnea syndrome: an update for 2007. An American Academy of Sleep Medicine report. Sleep 2008 Jan 1;31(1):141–7. [PubMed: 18220088]
46. Garber AM, Tunis SR. Does comparative-effectiveness research threaten personalized medicine? N Engl J Med 2009 May 7;360(19):1925–7. [PubMed: 19420360]