Auto-Titrating Versus Standard Continuous Positive Airway Pressure for the Treatment of Obstructive Sleep Apnea: Results of a Meta-analysis

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Study Objective: To compare the effectiveness of auto-titrating continuous positive airway pressure (APAP) versus conventional continuous positive airway pressure (CPAP) in reducing the apnea-hypopnea index (AHI), reducing the mean airway pressure, improving subjective sleepiness, and improving treatment adherence in patients with obstructive sleep apnea (OSA).

Design: Meta-analysis and metaregression of published randomized trials comparing APAP to CPAP.

Setting: N/A.

Participants: N/A.

Interventions: N/A.

Results: We identified 9 randomized trials studying a total of 282 patients. Compared to CPAP, there was no significant advantage of APAP in reducing AHI or sleepiness (pooled APAP-CPAP posttreatment AHI and Epworth Sleepiness Scale score = 0.20 events per hour, 95% confidence interval: [-0.74, 0.35], and -0.56 [-1.4, 0.3] respectively). The use of APAP reduced the mean applied pressure across the night by 2.2 cm water [1.9, 2.5] compared to CPAP. Adherence with therapy was not substantially improved with APAP; pooled estimate of improvement was 0.20 hours per night ([0.16, 0.37], P = .28) using a random-effects model.

Conclusions: Compared to standard CPAP, APAP is associated with a reduction in mean pressure. However, APAP and standard CPAP were similar in adherence and their ability to eliminate respiratory events and to improve subjective sleepiness. Given that APAP is more costly than standard CPAP, APAP should not be considered first-line chronic therapy in all patients with OSA. However, APAP may be useful in other situations (eg, home titrations, detection of mouth leak) or in certain subgroups of patients with OSA. Identifying circumstances in which APAP is a definite improvement over CPAP in terms of costs or effects should be the focus of future studies.

Key Words: sleep apnea syndromes, therapy, meta-analysis, patient compliance

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INTRODUCTION

OBSTRUCTIVE SLEEP APNEA (OSA) IS CHARACTERIZED BY RECURRENT COLLAPSE OF THE UPPER AIRWAY DURING SLEEP RESULTING IN REPETITIVE EPISODES OF ASPHYXIA AND SLEEP FRAGMENTATION. OSA has a myriad of adverse effects, including high blood pressure, daytime sleepiness, a reduction in quality of life, and an increased risk of motor vehicle crashes.1,2

Continuous positive airway pressure (CPAP) therapy has emerged as the primary treatment for OSA. Standard CPAP devices deliver a constant positive pressure to the upper airway during sleep via a plastic face mask and tubing. This pressure acts as a pneumatic splint, preventing the upper airway from collapsing. In patients with OSA, CPAP is effective in eliminating obstructive events, reducing blood pressure, reducing sleepiness, and improving quality of life.3,4 CPAP levels are generally set to eliminate apneas, hypopneas, snoring, and flow limitation in all positions and sleep stages. Given that pressure requirements may change according to sleep stage and body position, for most of the night the set pressure may be higher than the minimum level necessary to maintain airway patency. A major limitation of CPAP therapy has been patient adherence.5

Recently, a variety of autotitrating positive airway pressure (APAP) devices have been developed. In contrast to standard CPAP, in which the applied pressure is constant throughout the night, APAP devices deliver variable pressure according to the needs of the patient.6 In particular, if obstructive events are detected, the device will increase pressure until events are eliminated. The device will decrease applied pressure if no events are detected over a set time period. The different models vary substantially from the standpoint of event-detection algorithm. Some devices may rely on monitoring a single signal while others use a combination of physiologic signals including snoring, flow, or impedance to detect airflow obstruction. Effectiveness of APAP in reducing obstructive airway events should be similar to that of CPAP. However, because the minimum pressure required to keep the airway open is used, the mean pressure applied across the night should be reduced when compared to CPAP. It has been hypothesized that this reduction in mean applied pressure may improve patient tolerance, thereby resulting in an improved adherence with the use of APAP compared to CPAP. Increased adherence may lead to a greater improvement in daytime sleepiness.

Although a number of randomized controlled trials of CPAP versus APAP have been published recently, it is unclear how CPAP compares to CPAP in terms of effectiveness (ie, reducing obstructive airway events and sleepiness), mean applied pressure, and patient adherence. This is partially a product of the small number of patients studied in many of these trials, which has made it difficult to make definitive conclusions regarding APAP efficacy. In addition, because of the small sample sizes, it has also been difficult to explore the influence of diversity in popula-
tion characteristics (eg, differences in responsiveness to APAP based on race, sex, age, apnea severity, and APAP and CPAP pressure).

To address these concerns and to update the state of knowledge in this area, we conducted a meta-analysis of data from randomized controlled trials of APAP versus CPAP therapy in patients with OSA. Meta-analysis is a commonly used statistical technique whereby the results of individual studies can be pooled by weighting them according to their standard errors. Furthermore, metaregression techniques can then be used to assess whether various study characteristics could account for the heterogeneity in outcomes among the studies. Because data from a number of studies are used, the precision of the pooled result is greater than each individual study. In particular, we wanted to (1) compare APAP and CPAP in terms of effectiveness in eliminating obstructive events, level of mean airway pressure, improvement in subjective sleepiness, and treatment adherence in patients with OSA and (2) identify any study characteristics that might explain variations in the outcomes in the different studies.

METHODS

Literature Search

A systematic computerized search of publications in the MEDLINE database from 1980 to July 2003 was conducted to identify all randomized controlled trials assessing the effect of APAP compared to CPAP in patients with OSA. The search terms used were the following: (CPAP.af. or positive airway pressure.af. or positive airways pressure.af. or positive pressure.af. or airway pressure.af.) and (autotitrating.af. or autotitrating.af. or autoadjusting.af. or auto-adjusting.af. or selftitrating.af. or self-titrating.af. or self-adjusting.af. or self-adjusting.af. or automatic.af. or auto.af.) and (clinical trial.pt or randomized controlled trial.pt). The suffix .af. signifies that the term was allowed to be in ‘any field’ and the suffix .pt. signifies the ‘publication type’ field. Bibliographies of retrieved articles, previous meta-analyses, and reviews, including a search of the Cochrane database, were also used to further identify relevant publications. Experts in the field were also contacted for information regarding studies that may have been overlooked. Only full-length original articles and not abstracts, reviews, or duplicate studies were included.

Literature Selection

The following inclusion and exclusion criteria were used: the study population was limited to adults with OSA, standard CPAP was directly compared to APAP, therapies were used for at least 2 weeks, and the study design was a randomized controlled trial. We did not include studies that involved only a single night of APAP titration (to assess CPAP pressure) followed by CPAP set at that pressure. Observational studies without a control group were excluded.

Data Abstraction and Study Characteristics

Data abstracted from each paper included the year of publication, study design (crossover versus parallel), number of subjects in each group, subject sex distribution, mean age, mean body mass index (BMI), baseline and posttreatment apnea-hypopnea index (AHI), mean applied pressure level, adherence with therapy, length of follow-up, name of the APAP device, and posttreatment Epworth Sleepiness Scale (ESS) score.7

Quantitative Data Synthesis

We attempted to assess whether there were significant differences between CPAP and APAP arms in terms of posttreatment AHI, posttreatment ESS score, mean applied pressure across the night, and adherence with therapy. The measure of treatment effect was the difference between APAP and CPAP arms in terms of these variables.

In using meta-analysis to combine data from different trials, the observed variability among the individual trial estimates are commonly due to 2 major sources. Within-trial variability results principally from variation among patients within each trial, measurement error in the trial, etc. When the total observed variation among the different trial estimates can be fully accounted for by this within-trial variability, then trial effects may usually be combined by means of fixed effects models, and the heterogeneity test (Q test) will not be found to be significant. One could then argue that, if infinitely many patients were to be included in each of the contributing trials, the resulting estimates from the different trials would be identical. However, another common source of variability among effect-size estimates arising from different trials stems from differences (heterogeneity) between the trials. These differences may be due to a large number of factors: protocol variations in techniques, patient populations, methods and durations of treatment, technology used, etc. In this case, even having infinitely many patients in each trial would still result in distinct effect-size estimates from the different trials. In this situation, the heterogeneity test (Q test) will generally be significant, indicating that in addition to the inevitable within-trial variation, there is definite evidence in the data of a significant between-trial variation that must be accounted for in the meta-analysis. One models the data, therefore, not to represent a single effect common to all the trials, but to reflect individual random effects, one for each trial. The goal of the analysis at this stage is to attempt to estimate the weighted average of these effect sizes across the variable trials. Recognizing the extra variability among the trials, and therefore using the random effects model, leads, of course, to a less precise pooled estimate for the overall effect, with a wider confidence interval (CI) than the fixed effects model would have yielded. Therefore, in our study, a fixed effects model was used if significant heterogeneity was absent (Q test not significant). If significant heterogeneity was present, the random-effects model of DerSimonian and Laird was applied.8

The pooled estimate and its 95% CI were graphed on a Forest plot, along with the estimates derived from the original studies. If significant heterogeneity was present, we used metaregression to determine if a variety of variables (eg, sex distribution, mean age, BMI, baseline AHI, severity of somnolence as assessed by baseline ESS, length of follow-up, CPAP/APAP pressure) could account for the heterogeneity. All statistical analyses were performed using Stata 5.0 (Stata Corporation, College Station, Tex).

RESULTS

A total of 57 studies were identified from the literature search. After reviewing the abstracts, we considered 10 of the studies to be appropriate for our analysis; these studies were obtained and further reviewed.9-18 One of these studies was subsequently excluded because it included data on patients previously reported elsewhere.18 The 9 remaining trials studied a total of 282 patients. All of these studies included measures of mean pressure and adherence. Seven of them reported posttreatment AHI, and 6 of them reported posttreatment ESS.

Characteristics of the 9 studies are shown in Table 1. All the studies enrolled relatively few numbers of subjects (range: 10-52). In general, the patients enrolled in the trials had moderate to severe sleep apnea (range of mean AHI at baseline: 27-59 events per hour) and were obese (range of mean BMI: 32-41 kg/m2). Three of these studies used a crossover design (110 subjects), and 6 used a parallel design (172 subjects). These 9 studies used 6 different models of APAP; these 6 APAP models differed in terms of the set of physiologic signals they monitored to assess upper-airway obstruction.

For the 3 crossover studies, the standard error of the intraindividual differences between APAP and CPAP arms were not reported in the published manuscript. Therefore, we contacted the authors of these studies directly to request these data. However, this information was provided for only 1 of the studies. Thus, for the 2 remaining studies, we estimated the standard error of the difference conservatively using the SEM in the 2 arms and assuming independence between them.

The primary variables of interest were the differences between APAP and CPAP arms in terms of (1) posttreatment AHI, (2) posttreatment ESS
score, (3) mean applied pressure, and (4) adherence. To estimate the pooled effect from these studies, meta-analysis was performed. For post-treatment AHI and ESS score, there was no significant heterogeneity in the studies ($Q = 7.52$ and $1.78$ respectively, $P = .28$ and $.88$, respectively), and thus, a fixed effects model was used. There was not a significant difference in posttreatment AHI after CPAP or APAP (pooled difference of posttreatment AHI of APAP-CPAP = -.20 events per hour, 95% CI [-0.74,0.35]). (Figure 1) Similarly, there was no difference in posttreatment ESS score (APAP-CPAP) pooled difference = -0.56, 95% CI: [-1.4,0.3]). (Figure 2).

For the difference in mean applied pressure with CPAP versus APAP, significant heterogeneity was present among the studies ($Q = 76.4$, $P < .001$). Therefore, a random effects model was used. Use of APAP was associated with a reduction in mean applied pressure of 2.2 cm of water (95% CI: [1.9,2.5]) compared to CPAP (Figure 3).

For the difference in mean adherence between CPAP and APAP, the $Q$ statistic was 14.48, $P = .07$. We decided to use a random effects model because the $Q$ statistic is relatively insensitive in detecting heterogeneity, and a $P$ value of less than .1 is usually considered significant. Adherence with APAP was not significantly greater than with CPAP (pooled estimate of APAP-CPAP adherence= 0.20 hours per night, 95% CI [-0.16,0.57], $P = .28$). (Figure 4).

We used metaregression to determine whether heterogeneity in mean pressure and adherence differences could be explained by various study characteristics. For pressure, publication year ($P = .005$), sex distribution ($P = .016$), and age ($P < .001$) were significantly associated with APAP/CPAP pressure. That is, APAP reduced mean pressure to a greater degree relative to CPAP in more recent studies, studies with a higher proportion of women, and studies with younger subjects. Notably, baseline mean BMI, AHI, and study duration were not associated with differences in pressure.

In contrast, only the mean age of the patients was significantly associated with adherence differences ($P = .037$); that is, studies with a lower mean age tended to favor APAP over CPAP. Of note, neither mean CPAP pressure

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**Table 1—Description of Included Studies**

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year of Publication</th>
<th>Patients, no.</th>
<th>APAP Device (Manufacturer)</th>
<th>Device technique</th>
<th>Study type</th>
<th>Follow-up in each arm, wk</th>
<th>Baseline AHI*, events/h</th>
<th>BMI†, kg/m²</th>
<th>Age†, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meurice</td>
<td>1996</td>
<td>16</td>
<td>Morphée Plus (Pierre Medical)</td>
<td>Apnea detection</td>
<td>Parallel</td>
<td>3</td>
<td>43.6 ± 5.0</td>
<td>34.2 ± 5.7</td>
<td>54 ± 11</td>
</tr>
<tr>
<td>Series</td>
<td>1997</td>
<td>24</td>
<td>Morphée Plus (Pierre Medical)</td>
<td>Apnea detection</td>
<td>Parallel</td>
<td>3</td>
<td>48.5 ± 3.8</td>
<td>36.4 ± 7.6</td>
<td>36 – 65†</td>
</tr>
<tr>
<td>Konerman</td>
<td>1998</td>
<td>48</td>
<td>Horizon (DeVilbiss)</td>
<td>Apnea and snoring detection</td>
<td>Parallel 12-24</td>
<td>36.9 ± 1.7</td>
<td>32.1 ± 5.6</td>
<td>54.5 ± 6.7</td>
<td></td>
</tr>
<tr>
<td>D’Ortho</td>
<td>2000</td>
<td>25</td>
<td>REM + Auto (Respironics)</td>
<td>Apnea and snoring detection</td>
<td>Crossover 8</td>
<td>57.8 ± 1.2</td>
<td>32 ± 5</td>
<td>57 ± 11</td>
<td></td>
</tr>
<tr>
<td>Hudgel</td>
<td>2000</td>
<td>33</td>
<td>Virtuoso (Respironics)</td>
<td>Snoring detection</td>
<td>Crossover 12</td>
<td>27 ± 4</td>
<td>40.6 ± 11.5</td>
<td>46 ± 11.5</td>
<td></td>
</tr>
<tr>
<td>Teschler</td>
<td>2000</td>
<td>10</td>
<td>AutoSet (Respironics)</td>
<td>Snoring, apnea, flow detection</td>
<td>Parallel 8</td>
<td>52.9 ± 8.1</td>
<td>33.8 ± 4.1</td>
<td>52 ± 6.3</td>
<td></td>
</tr>
<tr>
<td>Randerath</td>
<td>2001</td>
<td>52</td>
<td>Somnosmart (Weinmann)</td>
<td>Forced oscillation</td>
<td>Crossover 6</td>
<td>35.1 ± 3.6</td>
<td>32.4 ± 5.8</td>
<td>54.7 ± 10.1</td>
<td></td>
</tr>
<tr>
<td>Massie</td>
<td>2003</td>
<td>44</td>
<td>AutoSet</td>
<td>Snoring, apnea, flow detection</td>
<td>Parallel 6</td>
<td>N/A</td>
<td>32 ± 4</td>
<td>49 ± 10</td>
<td></td>
</tr>
<tr>
<td>Planes</td>
<td>2003</td>
<td>30</td>
<td>REM + Auto (Respironics)</td>
<td>Snoring, apnea detection</td>
<td>Parallel 8</td>
<td>59.1 ± 3.1</td>
<td>32.4 ± 6.5</td>
<td>54.3 ± 10</td>
<td></td>
</tr>
</tbody>
</table>

* Values are mean ± SEM.
† Values are mean ± SD.
‡ Value is a range.

APAP refers to auto positive airway pressure; AHI, apnea-hypopnea index; BMI, body mass index.

**Figure 1**—Effects of auto positive airway pressure (APAP) versus continuous positive airway pressure (CPAP) on posttreatment apnea-hypopnea index (AHI). A negative score indicates a more beneficial effect from APAP than CPAP. X axis: posttreatment AHI with APAP minus AHI with CPAP (events per hour of sleep); Y axis: studies reporting posttreatment AHI ordered by year of publication. The bottom diamond represents the pooled effect with the dashed line drawn through the mean of this estimate.
nor differences between APAP and CPAP pressure were significantly associated with adherence differences ($P = .52$ and $P = .27$, respectively).

**DISCUSSION**

Our meta-analysis compared the effectiveness of APAP versus standard CPAP in the treatment of patients with OSA. We had 2 major goals. First, we hoped to determine whether APAP was better than standard CPAP in terms of reducing AHI, improving subjective sleepiness, reducing mean applied airway pressure, or improving adherence. Second, we sought to determine if any study characteristics affected the effectiveness of APAP. Overall, although APAP use was associated with a reduction in mean applied pressure across the night (pooled estimate = 2.2 cm water pressure), posttreatment AHI, subjective sleepiness, and adherence were similar in both APAP- and CPAP-treated patients. Metaregression techniques allowed us to assess whether any study characteristics could account for the differences in outcome. Mean age was the only variable that explained part of the variation in adherence differences, with younger subjects demonstrating greater adherence with APAP. However, this finding must be interpreted cautiously because the effect was small (slope = −0.08) and the range of mean ages was fairly limited (46–57 years). Of note, neither mean CPAP pressure nor the magnitude of pressure reduction with APAP (ie, APAP-CPAP pressure difference) was significantly associated with adherence. This was somewhat surprising, as we expected that these subsets of subjects may have been the ones most likely to benefit from APAP technology.11

There are a number of limitations in our analysis that need to be acknowledged. First, there are important differences in the various APAP models, depending on the manufacturer. As can be seen from Table 1, the 6 devices used in the 9 clinical trials varied in terms of the physiologic signals measured. For instance, the Virtuoso measures snoring, while the Somnosmart relies on the forced oscillation technique to assess airway patency. Furthermore, the algorithm by which they detect events, and the manner in which they increase or decrease applied pressure, vary considerably. As such, the effectiveness and tolerability of one APAP model versus another may be very different, and, thus, pooling the results of studies using different models may be overly simplistic. That is, ineffective titration algorithms in certain models may have affected outcomes. This issue could be clarified by performing randomized studies that directly compare different models. To our knowledge, only one small study (N = 21) published in abstract form has tried to address this issue19 and found no substantial differences between 2 APAP devices. Further work in this area is clearly needed.

Second, we included studies from a wide time range (ie, publication years from 1996 to 2003) to generate our pooled estimates. That is, we combined data from studies using older and less-sophisticated devices to newer technologies. This may also be overly simplistic because technology usually improves over time, and, as such, currently available devices may be substantially better than older models. In our analysis, we attempted to account for this fact by using year of publication as a surrogate marker of possible improvement in APAP technology over time. The effects of publication year on various outcomes may be seen in Figures 1 through 4, where we have ordered the studies by year of publication. Surprisingly, although later models were more effective in decreasing mean pressure (as confirmed with metaregression), suggesting refinements in APAP technology over time, publication year was not significantly associated with improvements in other outcomes. However, given the relatively small number of trials in our analysis, it is possible that an effect of publication year may have been missed (type II error). Also, because only 3 of the studies (involving 126 patients) were pub-
lished during or after year 2001 (and thus used reasonably current models), the effectiveness of the latest APAP models is unclear. It is thus possible that future larger studies using the best available APAP technology may show an improvement over CPAP. However, the available data suggest that variables other than mean pressure may be more critical in determining patient adherence.

Third, the studies used in our analysis enrolled predominately obese patients with moderate to severe OSA, with a mean age from 46 to 57 years. Most studies excluded patients with significant chronic obstructive pulmonary disease, heart failure, or central apneas. Thus, the performance of APAP in milder degrees of OSA or in the presence of these comorbidities remains unclear.

Nevertheless, we believe our results extend and support those of the American Academy of Sleep Medicine’s practice parameters for the use of APAP devices.20 Recommendation 5 from this document advises that “certain APAP devices may be used in the self-adjusting mode for unattended treatment of patients with OSA.” We have shown that APAP is as effective as standard CPAP in treating patients with OSA and that, therefore, this technology is a reasonable therapy. However, given the greater costs of APAP, we believe that CPAP rather than APAP should be considered first-line therapy in most patients with OSA. However, there are likely subgroups of OSA patients who may do better with APAP rather than CPAP. This may include younger patients, patients intolerant of CPAP, or patients with position-dependent or sleep-stage-dependent OSA.18 Future randomized clinical trials to precisely identify these subgroups are required. Also, many APAP devices can detect mouth leak and AHI; these capabilities are not available on many conventional CPAP devices. In certain patients, this information may be very valuable and may justify the increased cost of APAP. The choice of whether to use APAP over CPAP in certain patients should ultimately rest on the judgment of the clinician.

Of note, our analysis was focused on comparing the effectiveness of APAP versus CPAP as long-term treatment of OSA. Overall, APAP did not seem to have significant advantages over CPAP as long-term therapy. However, APAP may be useful and cost-effective under different circumstances. For example, one potential use could involve using APAP to ascertain CPAP pressure requirements unattended in the home, obviating the need for a CPAP-titration study in the laboratory. Using APAP in this manner could allow initiation of treatment more quickly, reduce in-laboratory time, and reduce healthcare costs. Further studies addressing this hypothesis from the standpoints of cost-effectiveness, patient satisfaction, and benefit on other outcome variables (blood pressure, etc.) would be of value.

In our meta-analysis, compared to standard CPAP, APAP was associated with a reduction in mean applied pressure. However, APAP and CPAP were equivalent in terms of patient adherence and their ability to reduce AHI and improve subjective sleepiness. Given that APAP is more costly than standard CPAP, APAP should not be considered first-line chronic therapy in every patient with OSA. However, it is possible that APAP may be useful in subgroups of patients with OSA.19 Furthermore, APAP technology is rapidly changing; the use of newer more-sophisticated devices may eventually be shown to be an improvement over conventional CPAP. Future studies designed to evaluate the newest technology and to identify subgroups of patients with OSA who respond better to APAP are required. These studies could help determine precisely where APAP devices fit in the treatment algorithm of patients with OSA.

REFERENCES