CPAP washout prior to reevaluation polysomnography : a sleep surgeon's perspective

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Abstract

Purpose: Obstructive sleep apnea (OSA) is characterized by repetitive upper airway collapse during sleep, leading to decreased oxygen blood levels and arousal from sleep. The gold standard treatment option for moderate to severe OSA is considered continuous positive airway pressure (CPAP). In case primary treatment with CPAP fails, a re-evaluation of disease severity [by means of the apnea/hypopnea-index (AHI)] can be required. A subset of patients that prefer a CPAP alternative is still using CPAP until the re-evaluation polysomnography (PSG) and a so-called washout effect is not ruled out. The purpose of this study is to evaluate the evidence on the existence and duration of this washout effect and to evaluate its clinical relevance for current practice.
Methods: Literature search through MEDLINE and EMBASE databases
Results: An overview of currently available literature on this washout effect and the findings of 13 studies on this topic, are discussed.
Conclusion: There is some evidence that CPAP washout exists in patients with a stable BMI throughout the follow up period. However, the intensity and duration of this effect remains unclear. Within the limitations of the present study, it seems reasonable to maintain a washout period of one week, in case alternative treatments options are considered and especially when a baseline PSG (and subsequent repeat PSG after treatment) is needed in case of clinical trials.

Keywords: Sleep disordered breathing, obstructive sleep apnea, CPAP, CPAP withdrawal, CPAP washout, compliance

Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive upper airway collapse during sleep, leading to decreased oxygen blood levels and arousal from sleep [1]. Aside from a proper intake including medical history and a clinical examination, a full-night polysomnography (PSG) is the most comprehensive and reliable objective monitoring method for the diagnosis of OSA. The gold standard treatment option for moderate to severe OSA is considered continuous positive airway pressure (CPAP), with oral appliances and surgical therapies reserved for well-selected patients with mild to moderate disease or for those who fail or refuse to use CPAP [2,3]. The selection pathway for these non-CPAP therapies is often clinically guided by an ear-, nose and throat (ENT) surgeon.

Since a proper assessment of the treatment outcome after non-CPAP therapies is essential to further consolidate the role of these therapies in the treatment of OSA, obtaining reliable pre- and post-treatment PSG results is essential. A subset of patients that fail to continue CPAP use or wish to evaluate an alternative treatment for travel, business or leisure purposes, still try to use their CPAP machine up until several nights before their visit to the outpatient ENT clinic, as it is their only treatment option so far. For medical as well as medicolegal and insurance purposes, a re-evaluation of the severity of the disease is often deemed necessary. This will include not only medical history taking and performing a thorough clinical ENT examination including drug-induced sleep endoscopy (DISE), but also polysomnographic re-evaluation. The primary PSG often dates from longer than one year ago and one cannot assume the AHI to remain stable over time.

The question then arises what patients should be advised on the cessation of their current CPAP use prior to the re-evaluation PSG, also bearing in mind the ethical and medicolegal issues of CPAP cessation. Recent literature suggests that CPAP might have a temporary residual effect on OSA after withdrawal from therapy, the so-called “wash-out period” [4]. Therefore, it has been claimed that patients should stop their CPAP at least several days before the PSG is repeated. It has been suggested that without this washout period, the PSG result could be an underestimated level of the OSA severity by showing artificially low AHI, respiratory disturbance index (RDI), oxygen desaturation index (ODI) values. This washout phenomenon is an important issue from both the theoretical and the clinical perspective and this review aims at providing a clear overview of the available literature on this topic.

Material and methods

To identify papers for this review an extensive literature search was run electronically in the MEDLINE and EMBASE databases on 22 October 2013 by one researcher (JS). The following search terms were used CPAP AND OSA* AND withdrawal; nCPAP AND apnea AND residual, leaving 561 articles. In addition, articles were identified from the references lists of these papers. For the comparison of pre-CPAP and post-CPAP outcome, articles were included and analyzed when they enclosed information on OSA parameters before and after withdrawal from CPAP therapy. Studies in which long-term CPAP use (>1 month) was missing were excluded from the study. This resulted in a set of 13 studies that met the search criteria and were further evaluated (AV, LB).

The studies within the present search criteria investigated different objective and subjective outcome parameters. In order to compare these studies, an analysis was performed focusing on the AHI as reported in the studies.

Results

Overview of the Evidence

Most studies within the search criteria analyzed the severity of OSA during CPAP treatment and after withdrawal from CPAP. Even though comparing OSA pre-CPAP and post-CPAP was not the primary goal of these studies, some did mention PSG variables [i.e. AHI, RDI and ODI] before the start of CPAP treatment.

Because not all studies provided the same data, the studies were split up into different sets. First, the studies in which there was no significant body mass index (BMI) change before and after CPAP therapy were separated from the studies that found a statistically significant reduction of the BMI or failed to report BMI changes entirely.

Secondly, the studies that did calculate the significance for the mean AHI/RDI/ODI differences between pre- and post-CPAP were separated from those not reporting these statistical calculations. An overview of these studies can be found in table 1, with a bubble chart (figure 1) visualizing the number of nights off CPAP (x-axis), delta AHI/RDI (change in AHI/RDI; y-axis) and number of patients included in each study (circle area).

Figure 1 Bubble chart displaying three data dimensions: the number of nights "off CPAP" (x-axis) and the delta AHI or RDI (y-axis), with the circle areas proportional to the quantities of patients included in each study (also noted between brackets following the first author's name in the legend).

1) CPAP withdrawal studies with no significant BMI change

Significant AHI/RDI reduction after CPAP withdrawal

Leech et al.[5] included 17 patients who had CPAP therapy for a median period of 6 months. PSG on the night off-CPAP showed a significant improved average RDI (55/hour sleep) compared to before the initiation of treatment (91/hour sleep). Along with this finding, a significant improvement of the mean daytime oxygenation (PaO_2 in mmHg) was found before treatment with CPAP (69 mm Hg) compared with after withdrawal (82 mm Hg).

Kribbs et al.[6] studied sleepiness after CPAP withdrawal in 15 patients with moderate to severe OSA by performing a Multiple Sleep Latency Test (MSLT). These patients received CPAP therapy for an average of 2 to 3 months, after which a PSG after one 1 night without CPAP was conducted. The mean RDI post-CPAP (36.8/hour sleep) was significantly lower than before initiation of therapy (56.6/hour sleep).

Bonsignore et al.[7] focused mainly on cardiovascular parameters comparing 29 untreated OSA patients, 10 OSA patients on CPAP and 11 controls. Within the group of 10 OSA patients receiving CPAP (mean treatment duration 5.5 months) a significant improvement was found in the mean AHI after 1 night without CPAP (63/hour sleep) compared to before treatment (82/hour sleep).

A recent study by Young et al.[4] evaluated 42 OSA patients that received CPAP for an average of 4 months, dividing them into subgroups of mild/moderate (n=22) and severe OSA (n=20). On the test night (2nd night of withdrawal) there was no significant difference in the mild/moderate group in the mean AHI (pre-CPAP: 15.7/hour sleep, post-CPAP: 16.7/hour sleep). However, within the severe OSA group patients showed significant better AHI values upon withdrawal (pre-CPAP: 77.6/hour sleep, post-CPAP: 61.9/hour sleep).

Insignificant AHI reduction after CPAP withdrawal

Contrary to these findings, the study of Boudewyns et al.[8] (n=25) did not find a significant difference of the AHI after quitting CPAP therapy. On the first night of withdrawal, after 1 year of therapy, patients showed a comparable AHI (94.1 versus 93.6/hour sleep) before and after CPAP.

Another study that did not find a statistical difference before and after CPAP therapy was conducted by Rauscher et al.[9], in 21 OSA patients. In this study, patients using therapy for an average of 8 months were given CPAP for only the first part of the night. The hours of sleep after using CPAP for the first part of the night showed an improvement of the RDI (28.7/hour sleep) compared to before these patients were treated with partial CPAP therapy (53.9/hour sleep). However, this change was not significant.

Fiz et al. [10]studied 10 OSA patients, having received 2 years of CPAP, on nights 1-4 of withdrawal from therapy. On the first night after stopping CPAP, the mean AHI level rose to a level indicating a severe level of OSA (40.5/hour sleep), but less severe compared to pre-treatment (47.0 /hour sleep). Interestingly, on nights 1-4 following CPAP withdrawal AHI levels did not rise (i.e. night 1: 40.5/hour sleep; night 2: 44.1/hour sleep; night 3: 42.2/hour sleep; night 4: 35.8/hour sleep).

In 20 OSA patients, Yang et al. reported even higher RDI levels after withdrawal (pre-CPAP: 47/hour sleep, post-CPAP: 50 /hour sleep) compared to before treatment. Also in this study, there was no deterioration found after additional nights without CPAP (7th night of withdrawal, AHI: 50 /hour sleep).

2) CPAP withdrawal studies with a significant BMI change or without sufficient BMI data

AHI reduction after CPAP withdrawal

Sforza and Lugaresi [11] studied 30 patients receiving CPAP for at least 1 year, primarily focusing on results from the MSLT, while also accounting AHI levels. The mean AHI before treatment with CPAP (74.4/hour sleep) was significantly higher compared to the first night of CPAP withdrawal (61.1/hour sleep). However, the patients did show a significant drop in mean BMI (pre-CPAP: 33.3 kg/m^2; post-CPAP: 31.3 kg/m^2; P<0.001), possibly contributing to the AHI reduction.

A randomized controlled study by Kohler et al.[12] investigated 41 CPAP users of which 21 patients were randomized to subtherapeutic CPAP, i.e. CPAP withdrawal. The two-week period on subtherapeutic CPAP (AHI 33.8/hour sleep) was associated with a significant increase in AHI, ODI and number of arousals compared to the results of the therapeutic (continued CPAP) group (AHI 0.4/hour sleep). The rapid increase in AHI in patients withdrawn from CPAP was already visible within the first nights. The mean pre-treatment AHI in the therapeutic group was lower (36.0/hour sleep) than the in the subtherapeutic group (45.3/hour sleep), although this was not significant (p=0.155). The authors did not report follow-up BMI values.

Phillips et al.[13] focused primarily on changes in inflammatory parameters in response to withdrawal from CPAP in 20 patients. The results showed a difference in the mean RDI on the first night of withdrawal (26.7/hour sleep) as compared to before treatment with CPAP (46/hour sleep). The authors mention that the protocol was sufficiently short to effectively exclude changes in fat

stores or BMI. However, BMI data were not supplied. Interestingly in this study, sleeping without CPAP for another 6 nights showed a significant deterioration of the mean AHI compared to the first night without CPAP (7^{th} night: AHI 39.0/hour sleep, $P<0.005$).

Pankow et al.[14] studied the effect of discontinuation of CPAP on the blood pressure in 12 male patients with OSA and arterial hypertension. Baseline PSG showed a median AHI of 43.0/hour sleep and the PSG with CPAP demonstrated a positive therapeutic effect with a median AHI of 3.7/hour sleep. After withdrawal from CPAP for 7-9 days there was a recurrence of the AHI to a median of 32.0/hour sleep. No data on BMI differences were supplied.

Marrone et al.[15] found a significant improvement of the mean AHI in 13 patients after one night of CPAP withdrawal (64.6/hour sleep) as compared to the AHI before treatment (80.1/hour sleep). However, the authors also reported a significant decrease of the mean BMI (pre-CPAP: 33.7/hour sleep; post-CPAP: 32.6/hour sleep; $P<0.05$).

Discussion

Thirteen articles reporting CPAP withdrawal were assessed, focusing on AHI and/or RDI, before- and after withdrawal from long-term (>1 month) CPAP treatment. These studies mostly used the same or very similar definitions for the AHI and RDI as stated by the AASM.

Three of these studies failed to report BMI changes during this period and 2 studies found significant reductions in the mean BMI after CPAP-use. All these 5 studies showed an improvement in the AHI after withdrawal from CPAP compared to before treatment, of which 2 reported a significant drop in AHI. Importantly, these 2 studies were also the studies in which a significant decrease of the BMI was reported.

Of the remaining 8 studies reporting no significant change in BMI, 6 showed improved AHI levels post-CPAP compared to AHI levels before treatment, of which 4 reported significant differences [6,5,4,7]. Young et al. found this statistical difference only in the severe, and not the mild/moderate OSA subgroup [4]. Two studies showed an increase in the AHI after CPAP withdrawal compared to before treatment [8,18]. The reported increase in AHI in these two studies was very small (0.5-3/hour sleep).

A small amount of studies has been performed with the goal of evaluating the difference in OSA severity (using AHI or RDI) before- and after treatment with CPAP. Six studies [6,5,9,4,12,19] used the AHI or RDI as primary outcome measure. Other studies did report the AHI level pre-and post-CPAP, but used MSLT [11], respiratory effort [8], neurobehavioral performance [18] or cardiovascular parameters [20,13,14,7] as primary outcome parameters.

Studies that did not mention the AHI or RDI before- and after CPAP treatment were excluded from this review. Some of these studies did describe pre- and post-CPAP differences, but instead focused on parameters such as hypoxemia[21], stress hormones[22], blood pressure[23], snoring characteristics[24] and driving performance[25,26]. Another study[27] was not included because patients did not receive long-term CPAP treatment before the investigation.

From the thirteen studies matching the search criteria comparing AHI before and after CPAP-use, long-term use of CPAP showed to have an acute residual effect after withdrawal from therapy. Eleven out of thirteen studies reported a decreased AHI after withdrawal from CPAP, six of which reported a significant decrease.

There are several important considerations to be made in order to interpret these results. First, most studies have a small sample size (N varying from 10 to 30). Secondly, studies in which the BMI could have played a role in the AHI improvement were also included in the search results. Although the authors are aware that OSA severity is related to BMI[28,29], for the sake of comprehensiveness these papers were also taken into account. All six studies that showed a significant difference in OSA severity between pre- and post-CPAP, conducted the PSG at the first or second night of withdrawal. This suggests that it is likely that the AHI is lower directly after withdrawal and a washout effect is indeed to be expected.

Three studies did report results of the AHI on multiple days after withdrawal from CPAP. Yang et al.[18] conducted PSGs on the 1st and 7th night of withdrawal. Fiz et al.[19] repeated PSGs on nights 1-4 after withdrawal. Both studies do not show a deterioration of OSA after multiple days of withholding CPAP. In contrast to these results, Phillips et al.[12] found a significant deterioration of OSA comparing the 1st and 7th night post-CPAP.

The amount of time it takes before OSA maintains a reliable, stable level after quitting CPAP therapy remains unclear and might be individual-dependent as well. As one study showed a significant difference between 1 and 7 nights of CPAP withdrawal, it could be advised to withdraw treatment for at least 8 days before conducting a PSG.

There may be several explanations for this residual effect of CPAP after withdrawal. Various structures in the upper airway can contribute to the upper airway obstruction in OSA. The upper airway anatomy and its response to differences in the pharyngeal pressure is one of the key factors in the pathogenesis of OSA [30,31]. During CPAP treatment pharyngeal size increases[32], thus

facilitating airflow. Several articles suggest a structural change in airway anatomy due to long-term CPAP use as the main reason for the presence of a residual effect after therapy[9,4]. The theory states that because of extended friction of the upper airway in OSA, pharyngeal edema develops, thereby further decreasing the airway lumen. Long-term use of CPAP would decrease this pharyngeal edema, by reducing friction of the mucosa. Ryan et al.[33] performed a study on magnetic resonance imaging (MRI) pre- and post-CPAP in 5 OSA patients and found a significant increase in pharyngeal volume following CPAP therapy. This increase mainly occurred in the oropharynx. Another study[34] screened 24 OSA patients using cephalometry before- and after CPAP treatment. The mean posterior airway space was significantly increased in supine, but not in erect position. Unfortunately, this study did not use MRI. In contrast, Collop et al.[35] also investigating pharyngeal volumes using MRI, found no difference pre- and post-CPAP in 12 patients with OSA. As these results show, limited data exist on the change of upper airway anatomy due to CPAP use. As a result, no definitive conclusion can be drawn about the possible existence of a difference between pharyngeal volume before- and after CPAP treatment.

Another possible mechanism for the extended effect of CPAP on the AHI, is an increased ventilation control mechanism in response to CPAP therapy. According to this theory, long-term exposure to frequent low oxygen levels in OSA patients would blunt their arousal responses to hypoxemic episodes. This lowered threshold in the central nervous system can result in altered responses to obstructive respiratory events. Kimoff et al.[36] showed that long-term OSA resulted in a reduction of breathing frequencies in response to hypoxia. Also in individuals at high altitude with chronic hypoxemia, ventilation control mechanisms seem to be impaired[37]. Another study[38] showed how sleep deprivation significantly decreased ventilation responses to hypoxia. These findings suggest that long-term use of CPAP could counteract the altered neuronal threshold for arousal responses by reducing oxygen desaturations and facilitating sleep. This seems plausible regarding the dynamics of neuroplasticity, and could play an essential role in the cause of a wash-out effect after acute withdrawal from long-term CPAP therapy.

It is interesting to evaluate this matter from the sleep surgeon's perspective in particular, as residual effects of non-CPAP therapies, e.g. upper airway stimulation [39] or oral appliances, are not observed during drug-induced sleep endoscopy. The effect of these therapies seems to immediately disappear after the upper airway stimulation therapy is switched off or the oral appliance is taken out. The same applies to the jaw thrust, chin lift or similar maneuvers – these effects do not last. One hypothesis could be that in the studies evaluated in the present paper, CPAP was used for more than one month and therefore a more prolonged effect on upper airway structures and behavior could be anticipated.

Assessment of the quality of evidence and strength of recommendations as presented in this paper by means of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system accentuates the lack of randomized controlled trials, limited study populations, imprecision because of different outcome measures, and the inconsistency of study results [40]. Moreover, the main research focus of the present study was mostly a secondary outcome in the majority of the included studies. Furthermore, the balance between health benefits and harms of CPAP cessation and duration thereof was not explicitly considered in any of the included studies. This implies a relatively low quality of currently available evidence to substantiate a solid recommendation on this topic, resulting in a 2C grade of recommendation. Further research, preferable by means of randomized clinical trials, could contribute to more robust recommendations.

All in all, generalization of the present results is cumbersome, as the studies included only small numbers of subjects, presented variable measurements of respiratory events, discussed different periods of time to assess CPAP washout, and only a few of the included studies took BMI into account. However, addressing the initial research question, albeit within the limitations as previously mentioned, remains of clinical importance for any clinician treating OSA patients who failed or refused to use CPAP.

In conclusion, there is some evidence that CPAP washout exists in patients with a stable BMI throughout the follow up period. However, the intensity and duration of this effect remains unclear.

The studies assessed in this paper described rather small patient populations and to what extent other reasons for night-to-night variability were controlled for (e.g., sleep position in positional OSA, changes in the percentage obstructive, mixed and central events), is uncertain. Within these limitations, based on currently available literature, it might be reasonable to maintain a washout period, with approximately one week being a possible advisable period, in case alternative OSA treatment options are considered and especially when a baseline PSG (and a follow up PSG after treatment) is needed in case of clinical trials.

Conflicts of interest

All authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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