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CPAP with Pressure Relief during Exhalation (C-Flex+) is as Effective as CPAP in the Treatment of Obstructive Sleep Apnea

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Abstract

Purpose: Continuous positive airway pressure (CPAP) is the accepted therapy for obstructive sleep apnea (OSA). An expiratory pressure relief technology called C-Flex has been developed to improve the comfort of CPAP therapy. It provides a 2 mbar lower exhalation pressure and an additional flow-based pressure relief at the beginning of exhalation. The following study was conducted to investigate whether C-Flex was as effective as CPAP in treating OSA, and the patients' preference.

Methods: 60 newly diagnosed patients with OSA completed this double-blind controlled crossover-study. Patients were randomized to one night of C-Flex and one of CPAP under full attended polysomnography (PSG). A comfort visual analog scale (VAS) ranging from 0 to 10, with 10 being the highest comfort, was completed by all patients immediately after each PSG.

Results: There was no significant difference between the therapy modes in the apnea/hypopnea index (median 1.5 events/hour (h) with C-Flex (interquartile range (IQR) 0.7 to 3.6) *vs.* 1.7 events/h with CPAP (IQR 0.8 to 3.8), p=0.178). The sleep efficiency, sleep architecture and nocturnal oxygenation were also comparable. Most patients preferred C-Flex over CPAP (65%, p<0.001). C-Flex earned significantly higher ratings in the VAS (8.1 (7.2 to 9.0) *vs.* 7.0 (5.1 to 8.8), p<0.001).

Conclusion: C-Flex was as effective as CPAP therapy in treating OSA and patients preferred this mode of therapy.

Keywords: Obstructive sleep apnea; Continuous positive airway pressure; CPAP; Expiratory pressure relief; C-Flex+

Introduction

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder with a prevalence of 10% in women and 20% in men in high-income countries [1]. Repeated collapses of the pharynx lead to reductions or cessations of air flow [2]. These collapses can be caused by a small upper airway lumen, dysfunctional dilating muscles and unstable respiratory control [1].

The most important risk factor for developing an obstructive sleep apnea is obesity. Approximately 70% of the patients are obese [2]. Other risk factors include increasing age, male gender, craniofacial predisposition, and postmenopausal status in women [1,2].

The pathophysiology of OSA is not completely understood; however, there are proposed associations with increased activity of the sympathetic nervous system, activation of inflammatory pathways, endothelial dysfunction, abnormal coagulation, and metabolic dysregulation leading to insulin resistance and impaired lipid metabolism [3].

The health risks related to the presence of OSA are serious and many patients suffer from hypersomnia which can cause occupational problems [4] or increased chances for car accidents [5]. Severe obstructive sleep apnea leads to an increased risk of cardiovascular events especially stroke [6]. Untreated sleep apnea is also thought to be associated with hypertension [7] and atrial fibrillation [8].

OSA is also thought to be related to higher rates in depression [9]. Even increased cancer mortality has been suggested [10]. Sequelae generally appear to increase according to the severity of the sleep apnea, which is measured by the apnea/hypopnea index (AHI).

The reference standard for the diagnosis is attended cardiorespiratory polysomnography (PSG) [11]. The state-of-the-art treatment of moderate to severe OSA is the administration of continuous positive airway pressure (CPAP) with individually titrated pressure settings [12,13]. CPAP provides a pneumatic splint of the nasopharyngeal airways [14]. CPAP therapy improves the vascular function [15] and shows a reduced risk for cardiovascular events in long-term studies [16]. It also improves the objective and subjective criteria of daytime sleepiness, especially in patients with severe OSA and high levels of daytime sleepiness [17]. A major problem with CPAP is the low adherence rate. In a long-term study of a Swiss population, only 55% of the patients prescribed CPAP still used their device after 5 years. The same study also showed improved adherence with newer CPAP technologies and increased service and technical support [18]. Several new features were developed to provide more comfort during therapy as an attempt to improve adherence [19]. In general the risk of pharyngeal collapse is higher during inspiration and lower during expiration. Therefore, a high pressure is not necessary during expiration [20]. A new pressure regulating mode had been introduced to lower pressure dynamically during expiration. C-Flex+ (Philips Respironics,

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PA, USA) is a comfort feature applying the prescribed therapy pressure during inspiration and providing a 2 mbar pressure reduction during expiration in a dynamic way. There is a further pressure relief at the beginning of expiration based on pressure measurement as sensed by the machine. For the patient there is no difference handling a device with plain CPAP mode or with the additional C-Flex+ mode. In summary the added feature is a software inside the CPAP machine which senses the pressure and modifies the applied pressure of the machine to imitate a more 'natural' pressure form to improve patient comfort and thereby therapy adherence. The additional cost for the machine with C-Flex+ mode differs much between countries. While it is marginal in some countries, the difference is considerable in other countries depending on national policies. The pressure curve of the dynamic C-Flex+ compared to CPAP is shown in (Figure 1).

We conducted a study to systematically assess whether C-Flex+ was as effective as CPAP in treating OSA.

The primary endpoint for the study was the AHI. The secondary endpoints were the nocturnal oxygen saturation, total sleep time, sleep efficiency, sleep architecture (N1, N2, N3 and REM sleep), average pressure output and the patients' preference.

Methods

93 CPAP-naive patients were enrolled in a prospective, double-blind, randomized, controlled study. The patients were referred to the sleep laboratory of the Charité Universitätsmedizin Berlin Campus Virchow with suspected OSA for a diagnostic attended PSG and treatment if required. The study was approved by the Ethics Committee of the Charité Universitätsmedizin Berlin. All patients were informed on the study purpose and provided written consent to participate.

Following diagnostic PSG, several patients were excluded because they did not fulfill eligibility criteria for the study . After a conventional attended titration night to determine the adequate therapy pressure, patients were randomized to one night of C-Flex+ and one night of conventional CPAP under full attended polysomnography (PSG). A comfort visual analog scale (VAS) was completed by the patients immediately after each PSG. After the last night patients were asked to decide which night (therapy) they preferred to evaluate the perceived comfort of the pressure curve. The study design is shown in (Figure 2).

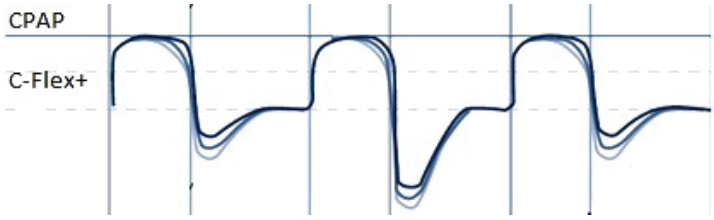

Figure 1: CPAP and C-Flex+ mode pressure curves over time [21]. The curves do show three subsequent inspirations and expirations. At the beginning of each expiration the particular relief drop in pressure is clearly observed.

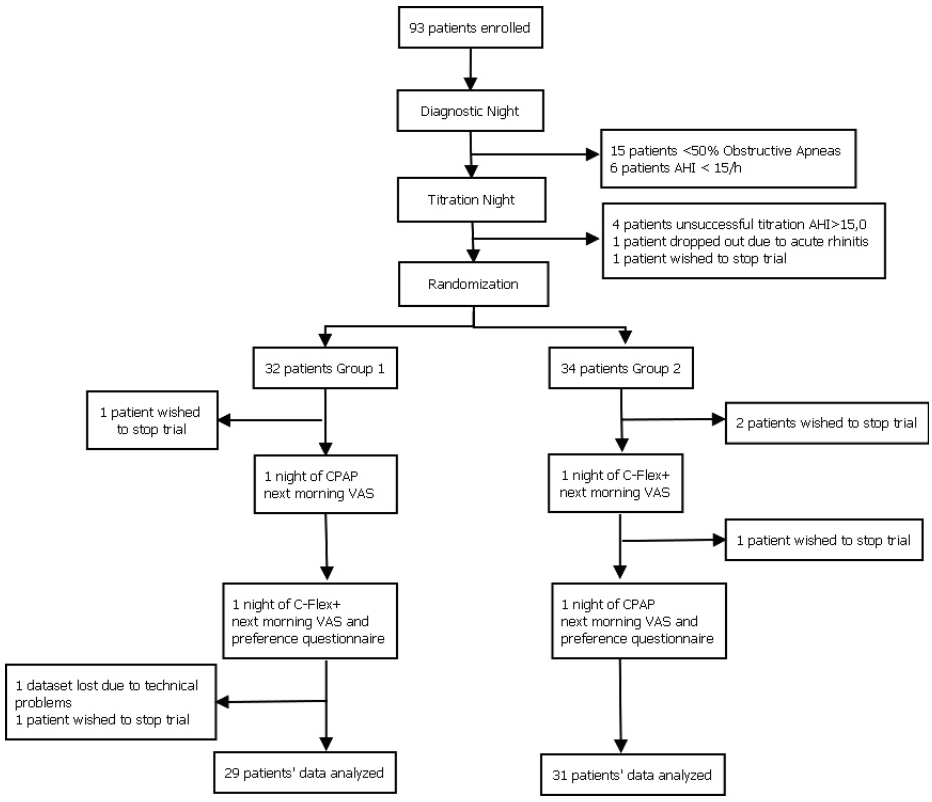

Figure 2: Flow chart of the study.

Only adult patients older than 21 years with a confirmed AHI > 15/hour (h) and > 50% obstructive apneas were included. They had to be able to provide consent as well as to follow the investigator's instructions concerning the CPAP device. Exclusion criteria were the inability to tolerate CPAP during the daytime session, failure of CPAP to adequately treat OSA during titration night (AHI > 15,0 under determined optimal pressure), medical contraindications to CPAP therapy such as sinusitis or surgery during the last 90 days, facial dermatitis or other skin lesions, untreated sleep disorders other than OSA like insomnia, periodic limb movements (PLM), restless legs syndrome (RLS), treated insomnia, intake of drugs affecting the central nervous system, previous experiences with CPAP, shift workers, participation in other clinical research during the last 4 weeks, or the patient requesting to withdraw from the study.

The data analyses were conducted with IBM SPSS Statistics Version 21. Differences between the treatments were analyzed using the Wilcoxon-signed-rank-test because the data were not distributed normally. Chi-square-test was applied to compare the patients' preferences.

Results

Sixty patients (48 males and 12 females) completed the study. For the baseline characteristics, see table 1. Based on the results of the titration night, the mean CPAP pressure was 8.7 ± 1.5 cmH_20.

As compared to the diagnostic night, both treatment interventions significantly improved the AHI, the obstructive, central and mixed apnea indexes, hypopneas index, minimum oxygen saturation and desaturation index (all p<0.001).The outcomes of both nights are listed in Table 2 and Figure 3

C-Flex+ earned significantly higher ratings by the VAS as compared to CPAP. 39 patients (65%) preferred C-Flex+, 12 patients (20%) preferred CPAP and 9 patients (15%) rated both C-Flex+ and CPAP equally comfortable (p <0.001). The rating values are shown in Figure 4.

Parameters	Median (Interquartile Range,IQR)
Age (years)	53.2 (46.8-59.7)
Height (m)	1.78 (1.70-1.86)
Weight (kg)	99.0 (84.3-115.8)
BMI (kg/m²)	31.6 (29.1-36.0)
AHI (events/h)	38.0 (27.5-61.4)
ESS (points/24)	12 (8 – 16)
BMI=Body-Mass-Index, ESS=Epworth Sleepiness Scale	

Table 1: Patient characteristics at baseline visit.

Discussion

This study showed that C-Flex+ and conventional CPAP were equally effective with respect to respiratory parameters and sleep architecture. The primary endpoint, the AHI, was significantly

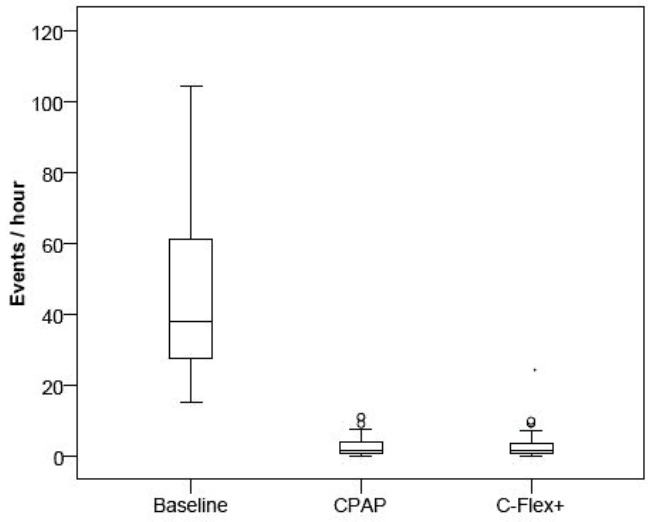

Figure 3: AHI at baseline, with CPAP and C-Flex+
Wilcoxon signed-rank test, both p<0.001 compared to baseline, no significant differences between the two modes. The circles symbolize outliers.

Parameter	Baseline	CPAP	C-Flex+	p Value
Apnea Index	23.1 (16.3-47.3)	0.9 (0.3-1.7)	0.3 (0.1-0.7)	<0.001
Obstructive Apnea Index	22.6 (11.5- 42.3)	0.2 (0.0-0.9)	0.0 (0.0-0.2)	<0.001
Central Apnea Index	0.9 (0.2-0.5)	0.4 (0.1-0.9)	0.2 (0.0-0.5)	0.034
Mixed Apnea Index	0.4 (0.0-3.4)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	n.s.
Hypopnea Index	10.4 (4.3-16.7)	0.6 (0.3-1.8)	1.0 (0.4-2.5)	n.s.
Apnea / Hypopnea Index	38.0 (27.5- 61.4)	1.7 (0.8-3.8)	1.5 (0.7-3.6)	n.s.
Minimum Saturation in %	80.0 (70.0-84.0)	91.0 (90.0-93.0)	90.0 (88.0-93.0)	n.s.
Oxygen Desaturation Index>4%	26.6 (17.8-49.4)	1.5 (0.6-3.9)	2.5 (1.1-5.0)	0.003
Mean Heart Rate	70.1 (65.5-78.6)	70.3 (64.7-75.0)	73.0 (65.3-78.5)	0.044
Total Sleep Time in min	-	375.0 (333.8-397.8)	373.0 (341.0-405.8)	n.s.
Sleep Efficiency in %	-	86.8 (81.1-91.4)	88.4 (81.5-91.8)	n.s.
N1 in %	-	15.2 (12.0-23.6)	14.8 (10.2-19.6)	0.008
N2 in %	-	38.7 (34.5-45.8)	39.5 (33.0-50.0)	n.s.
N3 in %	-	20.5 (15.5-27.6)	23.6 (15.2-27.8)	n.s.
REM in %	-	19.9 (15.8 -25.1)	22.0 (16.3-25.0)	n.s.
Arousal Index	-	11.2 (7.8-17.3)	11.9 (9.2-18.0)	n.s.
RERA Index	-	0.4 (0.0-1.0)	0.5 (0.2-1.3)	n.s.
Movement ArousalIndex	-	2.6 (1.3-6.2)	3.2 (1.6-4.9)	n.s.
PLM Arousal Index	-	1.0 (0.0 -2.8)	1.4 (0.0-3.1)	n.s.
n.s.= not significant, N=NREM, Non Rapid Eye Movement, REM = Rapid Eye Movement, RERA = Respiratory Effort-Related Arousals, *Wilcoxon signed-rank test* p-values refer to the differences between CPAP and C-Flex+. Parameters marked with "-" were not determined				

Table 2: PSG data of CPAP and C-Flex+, Median (IQR in parentheses)

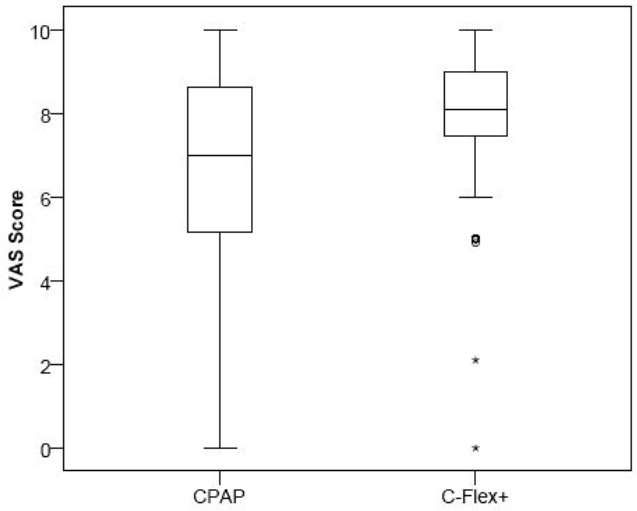

Figure: 4: Score in VAS with CPAP and C-Flex+ therapy showed that patients liked C-Flex+ more.
Wilcoxon signed-rank test, p<0.001. The circles indicate outliers and the stars indicate extreme outliers.

improved by both modes as expected. Between the two modes no significant difference could be detected concerning the AHI. By looking at the individual values we found that in three out of 60 patients the AHI was >4 events/hour higher with C-Flex+ compared to CPAP. This could be due to natural variability between nights or due to the more variable pressure with C-Flex+ mode.

Concerning most of the secondary endpoints there were no significant differences as well, though some differences nearly reached statistical significance.

In direct comparison with C-Flex+ there were significantly fewer total, obstructive and central apneas/h than with CPAP. There were no significant differences in mixed apneas/h, total sleep time, sleep efficiency and arousal index. There was significantly less stage NREM 1 (Non- Rapid Eye Movement) sleep with C-Flex+. With C-Flex+ there were significantly more oxygen desaturations > 4% /h and the heart rate was significantly higher compared to CPAP. Although these differences reached statistical significance there is minimal clinical significance of one additional desaturation per hour and a higher heart rate of less than three beats per minute, on average. The additional desaturation observed may be due to the same effect as reported with AHI: it could be either night-to-night variability or it could be due to the higher pressure fluctuations observed with the C-Flex+ pressure mode. For the heart rate values, CPAP lowered the mean heart rate significantly compared to baseline ($p<0.03$) whereas the mean heart rate with C-Flex+ compared to baseline heart rate did not show significant differences. Overall the differences in oxygen desaturation index (ODI) and in mean heart rate were statistically significant but cannot be considered as clinically relevant. Additional studies may clarify these findings.

However, these findings are surprising because most studies concerned with the predecessor comfort feature C-Flex (CPAP with expiratory pressure relief), did not find any significant differences between C-Flex versus conventional CPAP during attended PSG [22-28]. Only one study, conducted by Nilius et al., found statistically, but not clinically significant, differences in the number of central apneas/h with C-Flex (1.2 ± 2.5 versus 0.7 ± 1.0, $p = 0.04$) [20]. In contrary, our study showed a significantly lower central apnea index with C-Flex+ as compared to conventional CPAP.

In our study a significantly greater proportion of patients rated C-Flex+ as more comfortable than CPAP therapy. Two of the studies assessing C-Flex observed a significant preference for C-Flex as well [22,23]. A third one investigating the preference could not find a significant difference in the rating of the two [20].

However, based on data from this study, one cannot determine whether C-Flex+ leads to better long-term adherence. Studies assessing C-Flex showed that higher patient comfort ratings did not automatically lead to better adherence to treatment [22,23]. But Pépin et al. demonstrated that patients who showed low adherence to their CPAP device significantly improved their usage when changed to C-Flex [29] .

Therefore it would be desirable to perform a long-term study to see how C-Flex+ influences the adherence. If long-term studies investigating adherence to C-Flex+ are conducted they should have a duration of at least 3 months. Aloia et al. showed increasing differences in adherence between CPAP and C-Flex over this period of time. As time passed, fewer people in the CPAP group used their device while the people in the C-Flex group continued to use their therapy [24]. To check whether the incidence of cardiovascular consequences or even the cancer mortality changes with C-Flex+ compared to CPAP large trials and long-term observations are required.. This will require to establish a registry of CPAP and C-Flex+ users for well served regions.

In our study C-Flex+ proved to be as efficient as CPAP in treating sleep disordered breathing and can be an effective alternative for CPAP. Although we saw some statistical differences between C-Flex+ and CPAP, the differences did not have clinical relevance as both interventions adequately treated sleep -disordered breathing. Therefore C-Flex+ can be established as an alternative for CPAP therapy.

Acknowledgments

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