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Comparative Efficacy of Two Expiratory Pressure Reduction Systems in the Treatment of Obstructive Sleep Apnea

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Abstracts

Study Objectives: To assess whether two commercially available flow generators that reduce pressure during expiration have equivalent impact on respiratory events and sleep quality in the treatment of obstructive sleep apnea (OSA).

Methods: This was a prospective, randomized, single-blind, crossover, multi-center study of the S8 Elite Expiratory Pressure Relief (EPR) mode (ResMed) and the REMstar Pro C-Flex mode (Respironics). Among 88 adult, OSA-diagnosed patients screened for study eligibility, all experienced and compliant with continuous positive airway pressure (CPAP) in the C-Flex mode, 34 were eligible for participation. Titration studies utilizing C-Flex within the previous 12 months provided the baseline data. Subjects were randomized into two groups: one night on C-Flex mode followed by one night on EPR mode, or vice versa. After a desensitization period for subject acclimation to the EPR or C-Flex mode while awake, an overnight polysomnography was conducted to obtain data on Apnea/Hypopnea Index, oxygen desaturation (percentage time below 90%), Arousal Index, and Sleep Efficiency. A visual analog scale was used to assess patient comfort.

Results: Thirty-one subjects completed the study. Both modes were similar in efficacy for resolution of respiratory event parameters, improvement in sleep quality parameter and patient rated comfort. Mask leak was significantly lower with the EPR mode.

Conclusions: EPR is clinically equivalent to C-Flex in a controlled sleep laboratory setting. Less mask leak seen with EPR may potentially improve CPAP usage.

Introduction

Nasal continuous positive airway pressure (CPAP) is the standard of care for treatment of obstructive sleep apnea (OSA).[1–4] The major obstacle limiting the success of nasal CPAP has been the compliance with therapy. Serving as a pneumatic splint, CPAP is titrated to the critical opening pressure required to ensure patency of the upper airway during the entire respiratory cycle. Under the standard CPAP regimen, this critical pressure is fixed and continuous during both inspiration and expiration. Difficulty exhaling against a fixed pressure has been reported as one of the causes of low compliance rates among OSA patients in both short- and long-term studies.[5–10] However, the pressure needed to maintain an open airway is variable over the course of the respiratory cycle and, in association with decreasing lung volume, is likely lowest when OSA patients are exhaling.[11] Consequently, mismatches between the constant CPAP-delivered pressure and the lower critical pressure during exhalation are a recurring feature of the therapy and may contribute to the discomfort associated with exhalation. These instances of "pressure overdosing" may in turn lead to CPAP intolerance.

Newer technologies that decrease the pressure during exhalation such as REMstar Pro C-Flex mode (Respironics, Murrysville, Pennsylvania) have been developed to improve the acceptance of nCPAP therapy by patients who are expiratory pressure intolerant.[12] The flexible pressure technology that is present in C-Flex provides a lower pressure in the beginning of exhalation and then an increase at the end of exhalation to prevent airway collapse during the respiratory phase transition to inhalation. Despite its success in helping patients who are expiratory pressure intolerant, there remains a theoretic concern that the expiratory pressure drop during C-Flex may occur prematurely and lead to an expiratory pressure below critical opening pressure suggesting the need for improvement in such technology.

The present study is a comparative evaluation of two expiratory pressure reduction systems designed to provide enhanced comfort to the subpopulation of OSA patients who are expiratory pressure intolerant. Both the S8 Elite Expiratory Pressure Relief (EPR) mode (ResMed Corporation, Poway, California) and the REMstar Pro C-Flex mode offer pressure relief at initial active exhalation with C-Flex increasing pressure at the end of expiration and EPR increasing pressure at the beginning of inhalation. In clinical studies comparing pressure relief technology or auto-CPAP to conventional CPAP, both proved functionally equivalent to CPAP.[12–16] In this study, we compared EPR and C-Flex on respiratory events and sleep quality during one night of laboratory titration.

Methods

This was a prospective, randomized, subject-blind, crossover, multi-center study of two commercially available flow generators set to expiratory pressure reduction mode. The present study was conducted under an approved non-significant risk Investigational Device Exemption at two U.S. clinical sites. The study was approved by the Institutional Review Board at each institution. Study enrollment commenced in May 2005 and closed in November 2005.

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Table 1. Study Inclusion and Exclusion Criteria

Inclusion Criteria	*Exclusion Criteria*
Adult (≥ 18 years of age)	Recent sinus surgery (within 6 weeks of study entry)
Diagnosis of OSA (10% or less central events),baseline Apnea/Hypopnea Index ≥ 15 events/hour	Use of oxygen device
Attended diagnostic/titration study, using CPAP with C-Flex, within 1 year of study entry	Restless Legs Syndrome
Compliant CPAP/C-Flex use (defined as using C-Flex for ≥ 3 months for at least 70% of nights, for ≥ 4 hours per night, verified by data downloaded from own flow generator)	Central sleep apnea, defined as 10% or more of the events
Willingness to provide written informed consent	History of clinically significant epistaxis in the prior 6 months
	Preferential sleep during the day (e.g., nightshift worker, circadian rhythm disorder)
Pittsburgh Sleep Quality Index questionnaire score < 5 points	Travel through more than two time zones within 1 month of study entry
No concurrent participation in other clinical trials	Pregnancy
No concurrent medications that might affect sleep during study period	Any chronic or acute, life-threatening condition that participation in and completion of the protocol

Subjects and Study Design

Eighty-eight subjects were screened for study entry. Thirty-four subjects met the entry criteria and were enrolled into the study. The inclusion and exclusion criteria of the study are summarized in Table 1.

Eligible subjects were confirmed compliant with the REMstar Pro flow generator in the C-Flex mode via a review of data from the machine. Patients underwent an in-laboratory CPAP titration with C-Flex mode prior to study. Using a randomization table whereby subjects alternated first treatment, subjects were then randomized into one of two PSG study groups: one night on the REMstar Pro C-Flex mode and, within a 2-week window, one night on the S8 Elite EPR mode, or vice versa for device order. Table 2 summarizes the study visits and procedures.

Each subject was blind as to which device was being used. Blinding was achieved by covering the device used in the study, prior to the subject entering the room. Observation during the study by sleep technician assured integrity of the blinding. Adjustments to CPAP pressure were permitted within the first 90 minutes of sleep on the first night only. Patients used the same mask during both nights. The AHI and desaturation time values were derived from the final pressure used during the adjustment period. Subjects were asked to sleep at least part of the night in the supine position during the titration studies.

Data Collection

The objectives of this study were to assess and document whether the two expiratory pressure relief modes are equivalent on resolution of respiratory events and improvement in sleep quality in the treatment of OSA. The specific respiratory event data collected, utilizing American Academy of Sleep Medicine criteria,[17] were (1) Apnea/Hypopnea Index (AHI) values and (2) percentage time oxygen desaturation <90% (O_2 desat). Sleep quality data collected were the Arousal Index (ArI) and Sleep Efficiency (SE) scores. A visual analog scale (VAS), composed of 8 questions, was used to assess subject comfort with the devices during sleep after each polysomnogram.[18]

Differences between Two Systems

The S8 Elite™ uses a pressure-based therapy system, whereas the REMstar Pro™ uses a flow-based method. In this study, the EPR mode was set to provide a 3 cm H_2O expiratory pressure relief and C-Flex was also set at 3 (arbitrary units).

There are differences between two expiratory pressure relief modes as depicted in figures 1 and 2 (see page 22). Figure 1 depicts a simulated breath in which the EPR pressure algorithm is detailed with both expiratory and inspiratory flow curves. EPR's pressure drop from fixed CPAP is triggered by a patient's 3 liters per minute (LPM) expiratory effort, and its pressure increase to maximum CPAP is triggered by a patient's 3 LPM inspiratory effort, within a 0.6-second window or rise time. EPR's Event Detection and Time-Out features automatically turn off EPR and revert to CPAP if breathing events such as apneas occur.

In contrast, as illustrated in Figure 2 (see page 22), REMstar Pro C-Flex mode triggers pressure relief by the patient's expiration, but it reduces pressure by varying amounts (i.e., proportional to respiratory effort). As a consequence, pressure drop may vary from patient to patient and breath to breath.

Table 2. Study Protocol Summary: Visits and Procedures

Consent	*Screening*	*PSG Night 1*	*PSG Night 2*
Historical data obtained	Pittsburgh Sleep Quality Index	EPR or C-Flex	EPR or C-Flex
Diagnostic and titration PSGs with C-Flex mode	Epworth Sleepiness Scale	Morning after, visual analog scale	Morning after, visual analog scale
	Compliance data downloaded from flow generator	CPAP pressure fixed after 90 minutes	CPAP pressure equal to final pressure at Night 1

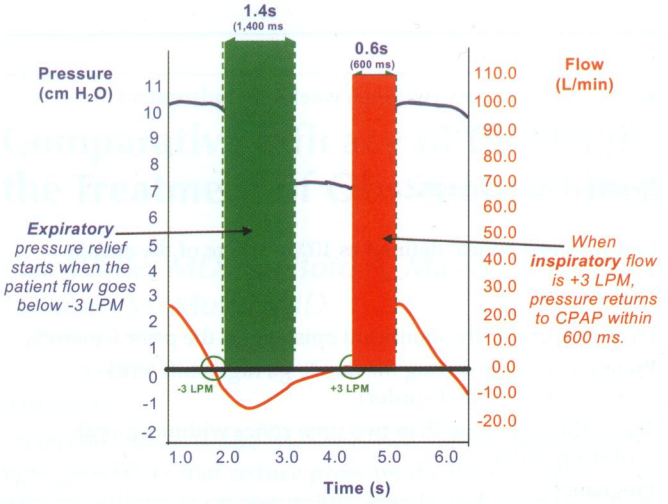

Fig. 1. The pressure algorithm during EPR mode shown during a simulated breath. EPR's pressure drop from fixed CPAP is triggered by a patient's 3 liters per minute (LPM) expiratory effort, and its pressure increase to maximum CPAP is triggered by a patient's 3 LPM inspiratory effort, within a 0.6-second window or rise time. EPR's Event Detection and Time-Out features automatically turn off EPR and revert to CPAP if breathing events such as apneas occur.

C-Flex returns to its set point CPAP pressure after a programmed amount of time. In other words, it is triggered by a programmed timer rather than by the patient's expiratory effort. As such, a patient may still be in the expiratory phase of respiration when the pressure increases, potentially resulting in discomfort and negatively affecting the respiratory cycle and work of breathing.

Statistical Analysis

The goal of the study was to demonstrate equivalence of the EPR versus C-Flex modes for respiratory events and sleep quality based on a predetermined acceptable difference for each parameter. Equivalence was defined as: (1) AHI using EPR equivalent to C-Flex if the mean difference is within 2 events/hour and (2) O_2 desat using EPR will be equivalent to C-Flex if the mean difference is within 4%. (3) ArI using EPR will be equivalent to C-Flex if the mean difference is within 10 events/hour and (4) SE using EPR will be equivalent to C-Flex if the mean difference is within 10 percentage points. (5) Comfort as determined by VAS scale ratings.

A paired t-test, using the clinically relevant margins, was used to test the significance of the mean difference values. A p-value of 0.05 or less was sufficient to conclude that the EPR mode is not inferior by the clinically relevant margin.[19]

Results

Demographics and Clinical Characteristics

Sixteen of the 34 subjects were randomized to EPR on their first night, 17 to C-Flex, and 1 subject withdrew before randomization. Thirty-one evaluable subjects completed the study. Three subjects withdrew after enrollment into the study. The first subject was withdrawn due to a learning curve associated with the protocol procedures for the lab staff. Second subject was withdrawn due to pressure intolerance during the second sleep study with C-Flex and the third subject was not randomized due to a need for bi-level therapy, based on the results of the titration study. Baseline demographic data and clinical characteristics of the 31 study subjects are summarized in Table 3.

PSG Findings

Prior to statistical analysis of the data, a 2-way analysis of variance was conducted to determine if device order had an effect on the outcomes. No order effect was found for any of the parameters. Statistical analyses of the two primary objective endpoints for respiratory events, AHI and percentage time oxygen desaturation <90%, revealed that the two devices are clinically equivalent. Table 4a and 4b provides results for the respiratory endpoint analysis. The percent of subjects achieving AHI less than 5 events/hour and the percent of subjects maintaining a SpO_2 of 90% or higher throughout the night were similar for both modes. Sleep quality endpoints analyzed include the ArI and sleep efficiency (SE) (see Table 4c). Statistical analyses of these parameters revealed that the two devices are clinically equivalent.

Mask leak data, as reported by the devices in liters per minute (LPM) and calculated by pressure delta over time, were also analyzed (Table 5, see page 24). Subjects on EPR who had mask leak averaged 7.28 LPM (0.12 liters/sec), whereas subjects on C-Flex with mask leak averaged 28.49 LPM (0.47 liters/sec). The data show a significant mean difference (–21.2 LPM) in quantity of leak between the EPR and C-Flex modes.

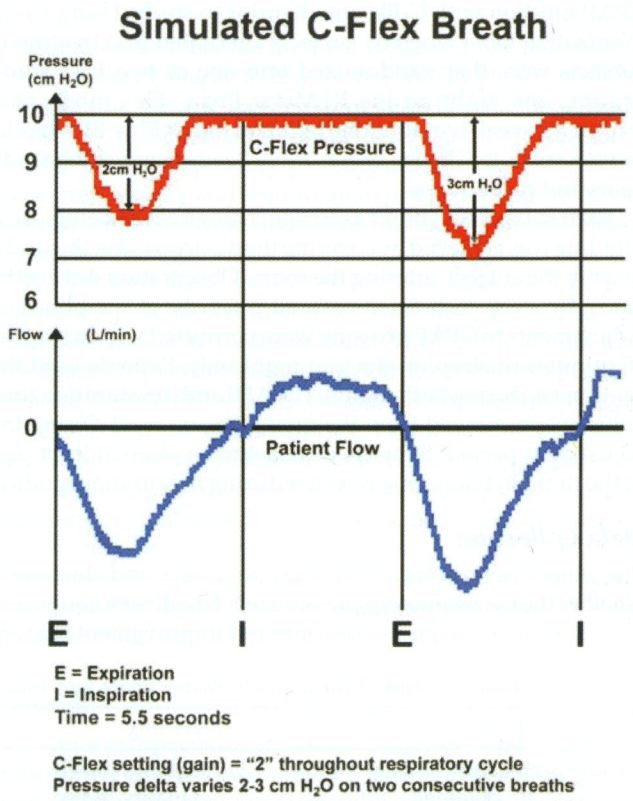

Fig. 2. The pressure and flow pattern during C-Flex mode. The C-Flex triggers the pressure relief with the patient's expiration, but it reduces pressure by varying amounts proportional to respiratory effort. C-Flex returns to its set point CPAP pressure after a programmed amount of time.

Table 3. Patient Demographics and Clinical Characteristics

Demographics	
Gender	%
Males	71.0%
Females	29.0%
Age (years)	*Mean ± SD*
Range: 35–80	54.7±11.5
Body Mass Index (kg/m²)	*Mean ± SD*
Range: 23.5–62.4	36.1±9.0
Race	%
White	90.3
Non-White	9.7
Clinical Characteristics	
Sleep History	*Mean ± SD*
ESS scores	
Range: 0–15	5.9±3.7
Prescription Information	
CPAP Pressure (cm H_2O)	*Mean ± SD*
EPR	12.0 ± 3.0
Range: 6–18	
C-Flex	12.0 ± 3.0
Range: 6–19	

A subset analysis was done on those patients who experienced high leak (>24 LPM) while using C-Flex. These subjects averaged 39.2 LPM (0.65 liters/sec), whereas their mask leak on EPR averaged 10.6 LPM (0.18 liters/sec). The data show a significant mean difference (–28.7 LPM) in quantity of leak between the EPR and C-Flex modes. Despite an improvement in leak with EPR, patients in this high leak subset that used EPR mode did not have improved sleep efficiency versus those in this high leak subset that used C-Flex.

One explanation for the significant leak differences between EPR and C-Flex modes may be due to a difference in the methods of reporting leak data between the devices. ResMed's EPR devices report "true leak" which is "total system leak" minus intentional leak (i.e., for CO_2 venting) from the specified mask that is used by the patient and programmed into the device. Respironics' C-Flex devices report only "total system leak". Estimating "true leak" from the C-Flex device requires use of the device manuals to derive an approximation of "true leak" based on the pressure setting; it is noted that this true leak value will vary based upon mask used and system set-up so the calculation is difficult to equilibrate. In summary, raw device leak data was used for comparison purposes in this study as this was the only leak data available; the calculation and reconciliation of "true leak" estimates from the Respironics C-Flex device fluctuated widely for the same mask and pressure setting and thus it was not possible to calculate leak measurements corresponding to those of the EPR device.

Analysis of Subjective Patient Comfort

Patient subjective comfort for the full cohort and the subset of patients with high leak (>24 LPM) on C-Flex was assessed using an 8-question VAS questionnaire previously published. A high score represents a positive response. Descriptive statistics are presented in Table 6 and reveal similar results for the two

Table 4. The Effect of EPR and C-Flex on Respiratory Parameters and Sleep Quality

4a. Respiratory Events

Endpoint	*N*	*EPR: Mean ± SD*	*C-Flex: Mean ± SD*	*Difference: Mean ± SD (95% CI)*	*Mu (Acceptable Difference)*	*P value*	*Equivalent*
AHI (events/hr)	31	5.0 ± 6.3	5.7 ± 6.2	–0.7 ± 4.6 (–2.4 – 1.0)	+2	.0001	Yes
O_2 Desat (% time <90%)	31	1.0 ± 1.9	1.6 ± 7.2	–0.7 ± 6.4 (–3.0 – 1.7)	+4	.0004	Yes

AHI: number of apneas/hypopneas per hour of sleep.

Oxygen desaturation time: determined as total time during sleep study with desaturations less than 90%. Result reported as a percentage of time that the qualifying desaturation occurred.

4b. Respiratory Event Thresholds

	EPR: % (n/N)	*C-Flex: % (n/N)*
Percentage of patients achieving an AHI <5 Events/Hour	61.3% (19/31)	61.3% (19/31)
Percentage of patients achieving Minimum SpO_2 of 90% or Higher	29.0% (9/31)	41.9% (13/31)

4c. Sleep Quality

Endpoint	*N*	*EPR: Mean ± SD*	*C-Flex: Mean ± SD*	*Difference: Mean ± SD (95% CI)*	*Mu (Acceptable Difference)*	*P value*	*Equivalent*
ArI (events/hr)	31	22.3 ± 9.6	23.4 ± 8.9	–1.2 ± 7.4 (–3.9 – 1.5)	+10	<.0001	Yes
SE %	31	80.8 ± 15.7	79.9 ± 13.5	1.0 ± 15.2 (–4.6 – 6.5)	-10	.0004	Yes

Arousal Index (ArI): number of EEG arousals per hour of sleep. An EEG arousal is defined as a 3 second return to alpha (awake) EEG.

Sleep Efficiency (SE): total amount of sleep divided by total sleep time (TST).

Table 5. Comparison of Average Leak (LPM) between Modes

	N	*EPR: Mean ± SD*	*C-Flex: Mean ± SD*	*Difference: Mean ± SD(95% CI)*	*P value*
Average Leak (LPM)	19	7.28 ± 11.85	28.49 ± 19.45	–21.22 ± 18.08 (–29.9 – 12.51)	.0001

*EPR is significantly lower in leak than C-Flex, paired t-test with mu=0, p < 0.0001

devices both for the full cohort. No adverse events occurred with any subject during their participation in the study.

Discussion

Our study shows that the two CPAP devices that provide pressure relief technology are comparable in terms of alleviating respiratory events and sleep fragmentation. The findings of the EPR versus C-Flex study demonstrate that in a sleep laboratory setting of PAP therapy, the EPR mode is equivalent to the C-Flex mode in providing both effective OSA therapy and comfort based on AHI and O_2 desaturation analysis as well as VAS data collected in the study. Both modes were similarly effective in treating respiratory events and resolution of respiratory event related hypoxemia.

The additional finding of significantly less leak for subjects on EPR versus C-Flex ($p < 0.0001$) may be relevant as leak is a potentially salient comfort-compliance issue. As the subjects used the same mask with each device, the difference in leak is likely attributable to the differences in devices. Although EPR and C-Flex report leaks differently (total vs. intentional), the differences we observed in leak values between two devices cannot be explained by the differences in leak reporting styles. Air leak has been shown to contribute to sleep fragmentation and diminished sleep quality and thus adversely impact adherence to CPAP therapy.[20] Furthermore, air leak may interfere with the pressure triggering mechanisms by compromising the PAP device algorithms and lead to impaired monitoring of the airflow, dysynchrony and intolerance to pressure.[21–23] While our data did not show any difference in sleep fragmentation or other clinical outcomes between the two devices, we believe that the differences in leak between devices warrants further investigation due to theoretical benefit of reduced leak.

In patients with high air leak, our results showed a trend towards a higher success rate in achieving an AHI less than 5 events per hour when EPR mode was administered. This may be attributed to the increased ability of EPR to control expiratory pressure, including the apnea detection circuit and the 3-second time-out components with the feature to return to the preset CPAP setting if a high leak occurs. The EPR mode is turned off in the presence of an apnea, reverting to the fixed-pressure CPAP mode. These features may help to reduce mouth opening and leak, which were confirmed in our study.

Although our study did not find significant improvement with EPR over C-Flex in clinical efficacy and patient comfort, this evaluation was conducted in the laboratory over the limited duration of two nights. Longer-term, comparative follow-up studies are needed to evaluate the EPR versus C-Flex modes on an ongoing basis for the impact of efficacy on treatment compliance. In-home use of the devices over a longer term may yield significant differences, particularly in patients who experience high leak on C-Flex.

Acknowledgments

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Table 6. Subjective Patient Comfort during Sleep between the Two Modes: VAS Questionnaire (For all patients)

	EPR: Mean ± SD	*C-Flex: Mean ± SD*	*Difference: Mean ± SD (95% CI)*
	N = 31	N = 30	N = 30
Q1. How satisfied were you with CPAP?	76.8 ± 22.6	79.8 ± 13.5	–3.6 ± 19.9 (–11.0 – 3.9)
Q2. How satisfied were you with the mask?	79.1 ± 20.4	81.8 ± 14.9	–2.9 ± 16.6 (–9.1 – 3.3)
Q3. How refreshed did you feel after waking in the morning?	72.9 ± 20.1	66.8 ± 19.8	6.7 ± 22.1 (–1.6 – 14.9)
Q4. How restful was your sleep?	69.4 ± 21.9	64.5 ± 18.5	4.5 ± 24.4 (–4.6 – 13.6)
Q5. How easy was it for you to get to sleep?	78.8 ± 19.4	69.4 ± 24.9	8.8 ± 26.9 (–1.2 – 18.9)
Q6. How easy was it to stay asleep during the night?	68.1 ± 24.6	67.9 ± 22.6	–0.8 ± 28.9 (–11.6 – 10.0)
Q7. How minimal was the mask leak you experienced?	75.3 ± 26.8	76.0 ± 24.7	–1.5 ± 28.6 (–12.1 – 9.2)
Q8. How comfortable was the amount of pressure from the flow generator?	83.5 ± 17.4	82.8 ± 17.6	0.3 ± 19.8 (–7.1 – 7.7)

* A high score represents a positive response

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