Work of Breathing in Fixed and Pressure Relief Continuous Positive Airway Pressure (C-Flex™): A post hoc Analysis

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Keywords

Work of breathing · Positive end-expiratory pressure · Obstructive sleep apnea · Inspiratory duty cycle · C-Flex™ · Pressure relief continuous positive airway pressure · Body mass index

Abstract

Background: Expiratory pressure relief continuous positive airway pressure (pressure relief CPAP; C-Flex™) causes increases in inspiratory duty cycle and shortening of expiratory time. It has been suggested that these changes are caused by an increase in work of breathing. **Objectives:** We studied the effects of C-Flex on work of breathing and intrinsic positive end-expiratory pressure as compared to fixed CPAP. **Methods:** Work of breathing was analyzed in 24 patients with obstructive sleep apnea during treatment with fixed CPAP and C-Flex with 3 different pressure relief settings in a randomized order during rapid-eye-movement (REM) and non-REM sleep. Work of breathing was assessed on a breath-by-breath basis using a piezoelectric esophageal pressure catheter and a pneumotachograph for measuring airflow. **Results:** We found there was no increase in inspiratory work of breathing observed using C-Flex compared to

fixed CPAP. Instead, we found a linear decrease in inspiratory work of breathing with increasing pressure relief, with a mean difference of 1.22 J/min between CPAP and maximum pressure release (C-Flex 3; 90% of the value with nasal CPAP); however, the decrease was not statistically significant. The decrease in inspiratory work of breathing associated with C-Flex has a significant inverse correlation with BMI. **Conclusions:** The C-Flex technology does not change work of breathing but shows a tendency towards a reduction of inspiratory work of breathing in patients with a lower BMI using higher C-Flex. The effect is probably caused by diminishing airway resistance generated by the positive end-expiratory pressure. Our findings may lead to additional fields of application of the C-Flex technology, such as chronic obstructive pulmonary disease or muscular dystrophy.

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Introduction

Night-time continuous positive airway pressure (CPAP) is still the mainstay of treatment for patients with moderate-to-severe obstructive sleep apnea (OSA) [1–5]. The association of OSA with increased risk of traffic ac-

Fig. 1. Comparative measurements of continuous positive airway pressure (CPAP) ventilation and C-Flex (C-Flex 3) during the night. In the upper section, device pressure (P_{device}) can be seen. Flow (measured with a pneumotachograph) is displayed in the middle section, and the corresponding esophageal pressure (P_{es}) is shown in the lower section.

cidents, cardiovascular morbidity, and all-cause mortality underlines the necessity of long-term treatment [6–9]. In this context there is a need to focus on patients' acceptance, tolerance, and adherence. Depending on the respective definition of sufficient adherence, up to 40% of CPAP users show suboptimal adherence [10–16]. Previous studies have shown that adherence or nonadherence to CPAP is established early during the treatment [17, 18]. A dry mouth, an increased number of awakenings, and problems exhaling are the most important factors [19]. Apart from other technical improvements such as humidifiers and more sophisticated masks, a number of new technologies are now available. Expiratory pressure relief techniques in particular aim to make exhalation more comfortable and thus optimize treatment adherence by improving comfort [20]. C-Flex™ (Philips Respironics, Murrysville, PA, USA) is a technology that reduces positive airway pressure in the initial phase of expiration on a breath-by-breath basis in proportion to a patient's expiratory flow rate. There are 3 different, gradually increasing levels of pressure relief, with a maximum drop of about 3 cm H₂O (3 mbar) [21] (Fig. 1).

Many studies compared C-Flex to conventional CPAP. In unselected patient groups, the overall efficacy of and

adherence to CPAP and C-Flex seem to be very similar [22–30]. C-Flex treatment has similarities with bi-level therapy, for which an increased occurrence of flow limitations has been described [31, 32]. This finding has led to the assumption that C-Flex is associated with an increased incidence of flow limitations.

However, in a prospective randomized study with 24 patients, our group demonstrated that there is no statistically significant difference regarding the occurrence of flow limitations with C-Flex compared to CPAP [33]. We also demonstrated that higher C-Flex gains were associated with a decrease in expiratory time in favor of the inspiratory duty cycle, while there was no significant change in tidal volume.

The mechanism of this change in duty cycle remains unclear. The available data might suggest an increase in the inspiratory work of breathing for increasing C-Flex gains, since a higher inspiratory duty cycle and higher inspiratory-to-expiratory time ratio are needed to achieve the same inspiratory tidal volume [34]. Such a change was demonstrated in case of flow limitations, which were not seen in any C-Flex setting [33]. Changes in duty cycle are predominant, while increases in breathing rate are much less pronounced.

Table 1. Patient characteristics

	Age, years	BMI	AHI before therapy	CPAP, cm H ₂ O
Mean $\pm$ SD	52.7 $\pm$ 8.5	33.4 $\pm$ 6	56.1 $\pm$ 30	9.1 $\pm$ 1.7
Range	36–65	25.2–49.1	19.7–126	7–13

AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure.

The finding of an increase in inspiratory time while the expiratory time was showing a consecutive drop and the breathing rate was exhibiting only a slight increase can also be interpreted in such a way that expiration is facilitated by a pressure relief technology in comparison to CPAP. This should then lead to a shorter time for adequate expiration. Since the increase in inspiratory time was not associated with an increase in tidal volume, more time may be left for smoother inspiration due to the reduced expiratory time. This might result in reduced work of breathing during inspiration, as a longer inspiratory time is available to inspire the same tidal volume, therefore requiring a lower peak inspiratory airflow.

Thus, it is also possible that C-Flex reduces the work of breathing during inspiration by diminishing the airway resistance generated by the intrinsic positive end-expiratory pressure (PEEPi). To answer the question as to how C-Flex affects the work of breathing, we reanalyzed the recorded data from our study published in this journal [33].

Study Design

Subjects and Equipment

Twenty-four patients (21 men, 3 women; age 52.7 $\pm$ 8.5 years; apnea-hypopnea index 54.0 $\pm$ 31.7; BMI 33.4 $\pm$ 6.0) with OSA diagnosed by standard polysomnography who had been assigned to effective nasal CPAP therapy successfully were examined. The study was performed using standard polysomnography in all patients. The patient characteristics are presented in Table 1.

CPAP treatment was started using the optimal effective mask pressure for each patient that had prevented apneas, hypopneas, and snoring during all sleep stages and in all body positions (particularly in the supine position). This effective pressure had been determined for each patient using standard polysomnography prior to the study night.

Mechanism of Pressure Relief CPAP (C-Flex)

The RemStar Pro C-Flex nasal CPAP device (Philips Respironics) can be used both as a CPAP device with fixed pressure and as

a CPAP device with expiratory pressure relief (C-Flex mode). The C-Flex device analyzes a patient's airflow and decreases mask pressure during the expiratory phase of each breath in proportion to the expiratory airflow according to the relationship (gain $\times$ flow) = P_{relief} . Gain can be adjusted by selecting 1 of 3 different pressure relief settings, with C-Flex 3 causing the largest expiratory pressure drop (largest gain). Accordingly, at the end of expiration, when the expiratory flow is decreasing, mask pressure is increased again and reaches the baseline therapeutic pressure, equivalent to that provided during inspiration.

Polysomnography

All polysomnographic recordings followed the guidelines of the American Sleep Disorders Association [35, 36]. To verify the stability and reliability of the recorded signals, a baseline recording during quiet wakefulness was performed over 15 min, with the patients lying supine in the lateral position. The patients were then allowed to fall asleep. The study protocol started once the patient had reached at least 2 min of continuous non-rapid-eye-movement (NREM) sleep, determined visually from the polysomnographic signals.

A heated pneumotachograph (model 3700 A; Hans Rudolph Inc., Kansas City, MO, USA) was attached to the nasal mask (Gel Mask; Philips Respironics) in order to measure all airflow. A Respironics RemStar Pro C-Flex device (Philips Respironics) was used for both CPAP and C-Flex treatment. After administration of a topical anesthetic, the piezoelectric esophageal pressure catheter (Gaeltec CTO-1; Gaeltec Ltd., Dunvegan, UK) was inserted through the nose into the esophagus.

Ventilation was measured using the pneumotachograph connected to a pressure transducer (TDP-2530; Föhr Medical Instruments, Seeheim-Jugenheim, Germany) placed between the nasal mask and the exhalation port of the mask system. The dead space between the mask and the pneumotachograph was approximately 120 mL. The pneumotachograph was calibrated prior to each recording. The flow signal was continuously displayed during all recordings, as was the infrared video monitoring. Thus, significant mask or mouth leakages could immediately be detected by the technician simultaneously observing the flow signal and the video picture. Only periods free of leakage were selected for analysis.

Study Protocol

Conventional CPAP or 1 of the 3 C-Flex pressure relief settings was applied for 15 min of continuously monitored, stable NREM sleep in a random order so that the 4 treatment modalities were randomly distributed throughout the entire night. During REM sleep, 5 continuous minutes were taken as 1 period, since REM sleep periods tend to be shorter than NREM periods. Three such 5-min REM sleep periods were recorded for each of the 4 ventilation treatments in order to balance the number of analyzable breaths during REM and NREM sleep. Thus, 60-min periods for both NREM and REM sleep were digitally recorded and analyzed offline later on. Periods for further analysis were selected by assessing signal quality. Patient 11 had no artifact-free period when using C-Flex 1 during NREM sleep. Patient 22 had no artifact-free period or period of sufficient length during REM sleep when using C-Flex 2 and 3.

The study was approved by the Ethics Committee of the University of Marburg. All patients gave written informed consent before inclusion in the study.

Fig. 2. Changes in mean values of tidal volume (Vol) and work of breathing (WOB) for each patient from continuous positive airway pressure (CPAP) to C-Flex 3 (upper left section: patients 4, 16, 18, and 22; upper right section: patients 2, 6, 9, 11, 14, 20, and 23; lower left section: patients 1, 3, 7, 8, 10, 12, 15, 17, 21, and 24; lower right section: patients 5, 13, and 19). The *x* axis represents the quotient of volume (C-Flex)/volume (CPAP), the *y* axis the corresponding quotient WOB (C-Flex)/WOB (CPAP).

Methods

Data Analysis and Associated Procedures

The clinical investigations were conducted in the period from March 10, 2005, to January 12, 2006, at Marburg University Medical Center. Data reanalysis was performed in the period from January to August 2015. Work of breathing and PEEPi were defined as outcomes of interest, and were considered in relation to time, volume, and body weight. Polysomnography was conducted and visually analyzed according to the standard criteria of the American Sleep Disorders Association [36, 37]. Apnea was defined as cessation of airflow for at least 10 s. Hypopnea was defined as a reduction in airflow by at least 50% for 10 s or as a reduction in airflow by less than 50% accompanied by a decrease in SaO_2 of at least 4% or arousal from sleep. The number of respiratory sleep disturbances per hour of sleep time was calculated and reported as the respiratory disturbance index.

Determination of Work of Breathing

Important progress in computerized breath-by-breath analysis enabled us to quantify work of breathing and accomplish a post hoc analysis of the existing data. The pressure signal as well as the flow signal were transmitted to polysomnography via amplified analog voltage signals and stored time-synchronously with the other polysomnographic signals for further processing. The algorithm for work of breathing estimation was implemented in the software EDF-Trace [38], a proprietary development, programmed with Borland Delphi.

Work of breathing (WOB) was calculated for each respiratory cycle (RC) as $\text{WOB} = \int -P \cdot dV$, where *P* represents intrathoracic pressure and *V* the tidal volume. RC limits were determined by positive zero-crossing of the airflow signal curve after application of a high-pass filter. By integrating the airflow signal, a trajectory

of tidal volume was obtained. For quantitative work of breathing calculation, a baseline readjustment of the calibrated esophageal pressure curve was necessary. Therefore, we marked the positions where the esophageal pressure drops and inspiration starts. These markers were considered as zero-pressure values. An interpolated baseline curve was calculated and subtracted from the esophageal pressure curve to obtain the surrogate for intrathoracic pressure.

Measurement of PEEPi

PEEPi was measured breath by breath as the negative intrathoracic pressure value at the starting point of inspiration, i.e., the positive zero-crossing of the airflow curve.

Calculation of Breathing Parameters and Work of Breathing

For each breath, the following parameters were calculated: duration of inspiration, expiration, and RC; inspiratory, expiratory, and total work of breathing; inspiratory, expiratory, and total volume; and PEEPi. Visual control and correction of all automatic calculations were performed by a physician (artifacts and episodes with mask leaks were removed). For this purpose, the evaluation software was equipped with a specific editor which displayed the Campbell diagram together with the particular results for each RC [39]. Thus, the scorer can mark or exclude RCs for further statistical evaluation and review the evaluation in detail.

Statistical Analysis

All parameters analyzed were tested for gaussian distribution with the Kolmogorov-Smirnov-Lilliefors test. Data found to be normally distributed are reported as means $\pm$ SD, while nonparametric variables are shown as medians and interquartile ranges. All comparisons between CPAP and C-Flex modes or between C-Flex modes were performed by applying 2-sided *t* tests for repeated measures. Statistical significance was assumed at $p < 0.05$ for all differences. Relationships between variables were tested for significance by the Pearson product-moment correlation. All statistical analyses were performed using the SPSS statistical packages (SPSS Inc., Chicago, IL, USA).

Results

There were no statistically significant differences in work of breathing between fixed CPAP and either of the 3 C-Flex levels. Figure 2 shows the magnitude of average changes in tidal volume and work of breathing for each patient when comparing CPAP and the highest C-Flex gain (C-Flex 3). As can be seen, 10 patients showed a decrease in both tidal volume and work of breathing when switched to C-Flex 3 (lower left grid), while 7 patients experienced an increase in both parameters (upper right grid) compared to CPAP. Only 4 patients had an increased work of breathing for a lower tidal volume; 3 patients showed a more efficient ventilation with an increased tidal volume accompanied by a decrease in work of breathing. In summary, C-Flex 3 led to an increase in tidal volume and correspondingly in work of breathing,

Fig. 3. Mean inspiratory work of breathing per minute ($\pm$ SD) during continuous positive airway pressure (CPAP) and the 3 C-Flex conditions.

Fig. 4. Mean inspiratory work of breathing per minute ($\pm$ SD) during continuous positive airway pressure (CPAP) and the 3 C-Flex conditions differentiated for rapid-eye-movement (REM) and non-REM (NREM) sleep.

Table 2. Inspiratory WOB per minute, inspiratory WOB per liter, and intrinsic positive end-expiratory pressure during CPAP and the 3 C-Flex conditions

Treatment and sleep stage	CPAP	C-Flex 1	C-Flex 2	C-Flex 3
Inspiratory WOB per minute, J/min	11.78 $\pm$ 4.21	11.65 $\pm$ 4.42	11.27 $\pm$ 4.80	10.56 $\pm$ 4.51
Inspiratory WOB per minute during NREM sleep, J/min	12.27 $\pm$ 4.19	11.94 $\pm$ 4.83	11.52 $\pm$ 5.11	11.09 $\pm$ 4.81
Inspiratory WOB per minute during REM sleep, J/min	11.29 $\pm$ 4.27	11.36 $\pm$ 4.06	11.02 $\pm$ 4.56	10.03 $\pm$ 4.22
WOB per liter, mJ/L	313.01 $\pm$ 84.71	310.71 $\pm$ 95.61	305.47 $\pm$ 108.88	290.35 $\pm$ 88.44
Intrinsic positive end-expiratory pressure, cm H ₂ O	1.97 $\pm$ 1.52	1.71 $\pm$ 1.42	1.56 $\pm$ 1.34	1.60 $\pm$ 2.25

Values are presented as means $\pm$ SD. Inspiratory work of breathing is differentiated for NREM and REM sleep. CPAP, continuous positive airway pressure; (N)REM sleep, (non-)rapid-eye-movement sleep; WOB, work of breathing.

or vice versa, in the majority of individuals (17 of the 24 subjects).

Due to heterogeneity of the patients' individual tidal volumes, we analyzed work of breathing in relation to time and volume in a second step. Thus, we achieved comparability of data.

Work of Breathing in Relation to Time

The results from the analysis of work of breathing are shown in Table 2. Because expiration is usually a passive process, the analysis showed quite small values for expiratory work of breathing for all the treatments. A comparison and grading of expiratory work of breathing therefore does not seem reasonable. Figures 3 and 4 show that inspiratory work of breathing decreases with increasing pressure relief, with a mean difference of 1.22 J/min be-

tween CPAP and C-Flex 3. However, these differences did not reach statistical significance.

Inspiratory Work of Breathing per Liter Ventilated Volume

Similar to the results for inspiratory work of breathing in relation to time, pressure relief did not produce a statistically significant change in work of breathing, and our data show no evidence for an increase in work of breathing with increasing pressure relief. There was, however, a trend observed in the direction of decrease with an increase in pressure relief (Fig. 5; Table 2).

Intrinsic Positive End-Expiratory Pressure

We observed a tendency towards a reduction in PEEP_i with increasing C-Flex gains similar to our findings for

Fig. 5. Mean work of breathing in relation to ventilated volume per liter ($\pm$ SD) during continuous positive airway pressure (CPAP) and the 3 C-Flex conditions.

Fig. 6. Mean intrinsic positive end-expiratory pressure (PEEPi) ($\pm$ SD) during continuous positive airway pressure (CPAP) and the 3 C-Flex conditions.

Fig. 7. Correlation analysis of body weight (BMI) and the ratio of work of breathing (WOB) per minute under the C-Flex condition (gain 3) divided by that under the continuous positive airway pressure (CPAP) condition for each subject. A significant reduction in WOB in correlation to lower body weight can be seen. Quot, quotient.

Fig. 8. Correlation analysis of body weight (BMI) and the difference between work of breathing (WOB) per minute with fixed continuous positive airway pressure (CPAP) and C-Flex (gain 3) for each subject. There was a significant reduction in WOB in patients with lower body weight ($p = 0.0382$). Diff, difference.

inspiratory work of breathing per minute and inspiratory work of breathing per liter. However, the reduction in PEEPi did not reach statistical significance as well (Fig. 6; Table 2).

Work of Breathing and BMI

Performing an analysis of the correlation between the C-Flex 3/CPAP ratio (Δ CPAP-C-Flex 3, respectively) and

BMI, we found that both (ratio and Δ) were correlated significantly with BMI ($p = 0.04$, $r = 0.42$, Fig. 7; $p = 0.03$, $r = -0.44$, Fig. 8). In other words, a lower BMI was associated with a decrease in inspiratory work of breathing comparing the C-Flex highest gain (C-Flex 3) with CPAP (Spearman rank correlation).

Discussion

C-Flex shows a tendency towards a reduction in work of breathing comparing the C-Flex highest gain (C-Flex 3) with CPAP when considering BMI as an independent factor. Published data suggest an increase in work of breathing using higher C-Flex gains, because of changes in inspiratory duty cycle and inspiratory time being associated with an increase in work of breathing [31, 32, 34, 40–42]. Our investigations show quite the reverse effect of pressure relief ventilation.

Without consideration of BMI effects, our data did not show any significant effect of pressure relief on work of breathing and PEEPi. There was, however, a trend for a decrease, and if a decrease in work of breathing occurs with pressure relief, a possible explanation could be that C-Flex may lead to smoother inspiration because a longer inspiration time is available to inspire the same tidal volume and therefore a lower peak inspiratory airflow is necessary. Consecutively, expiratory time decreases, which is consistent with the fact that C-Flex is characterized by expiratory pressure relief. Therefore, a reduced PEEPi – and thereby resistance – has a positive effect on work of inspiratory breathing when using C-Flex.

There may be additional areas of application of the C-Flex technology. Patients suffering from diseases associated with an increase in work of breathing, such as chronic obstructive pulmonary disease or muscular dystrophy, could benefit from the C-Flex technology and therefore be an interesting area for the investigation of effects on ventilation with pressure relief CPAP.

Since muscle activity decreases during REM sleep with a consecutive drop in minute ventilation and an increase in airflow resistance [43–45], possible advantageous effects of C-Flex should be clearly observable. Consistently, the strongest decrease in PEEPi in the comparison between CPAP and C-Flex could be observed during REM sleep (CPAP REM sleep PEEPi = 2.04 ± 1.19 cm H₂O; C-Flex REM sleep PEEPi = 1.48 ± 1.03 cm H₂O). Patients with a lower BMI seem to profit more than do obese patients with regard to a reduction in inspiratory work of breathing.

Our study has some limitations. Esophageal pressure monitoring distinctly impairs sleep quality [46, 47]. Nevertheless, more than 90% of our patients completed all measurements successfully. Furthermore, this method is considered the gold standard for determining work of breathing [48].

Body posture is known to have an effect on collapsibility of the upper airways [49] and on work of breathing –

for example, in case of a marked change of body position, such as elevation of the upper body. In this study, the sleep position was horizontal during the whole night for all patients. In addition, body position was closely monitored during the whole night via an infrared camera, ensuring no patient spent time sleeping on his stomach. Different postures of flat lying were possible (e.g., supine or lateral), but we did not expect relevant effects on work of breathing, as the patients were lying flat in all 3 positions.

The mean pressure in CPAP therapy was 9.1 ± 1.7 cm H₂O (range 7–11), which represents a common average therapeutic pressure [50]. We cannot say for certain that our results are representative of all pressure levels, but most CPAP investigations focus on mild-to-severe OSA (the mean apnea-hypopnea index in this study was 54.0 ± 31.7) without differentiation of therapy pressure.

Although because of the patients' heterogeneity any generalizations should be made with care, one of the strengths of our investigation is the considerable number of subjects examined; furthermore, to our knowledge it currently is the only study which investigated effects of the C-Flex technology on work of breathing. Conceivably, statistical significance could be achieved with a larger sample size, but considering the sophisticated study design we examined a rather large number of patients.

Conclusions

The C-Flex technology does not change work of breathing, but it shows a tendency towards a reduction in inspiratory work of breathing among patients with a lower BMI using higher C-Flex, which is probably caused by diminishing airway resistance generated by PEEP. Our findings may lead to additional fields of application of the C-Flex technology, such as chronic obstructive pulmonary disease or muscular dystrophy.

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Financial Disclosure and Conflicts of Interest

L. Jerrentrup states to have no financial involvement in any organization with a direct financial interest in the subject discussed in the submitted manuscript. S. Canisius currently is a part-time employee and holds stocks of Vectura Group plc, but he has no

direct financial interest in the subject discussed in the submitted manuscript. S. Wilhelm states to have no financial involvement in any organization with a direct financial interest in the subject discussed in the submitted manuscript. K. Kesper states to have no financial involvement in any organization with a direct financial interest in the subject discussed in the submitted manuscript. T. Ploch states to have no financial involvement in any organization with a direct financial interest in the subject discussed in the submitted manuscript.

C. Vogelmeier was a speaker at symposia and/or a member of scientific advisory boards for Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Grifols, Janssen, Mundipharma, Novartis, OmniaMed, and Takeda. T. Greulich was a speaker at symposia and/or a member of scientific advisory boards for Almirall, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Grifols, Mundipharma, and Novartis. H.F. Becker was a speaker at symposia for Philips Respironics, ResMed, Heinen & Löwenstein, and Novartis.

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