

The Supraglottic Effect of a Reduction in Expiratory Mask Pressure During Continuous Positive Airway Pressure

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Study Objectives: Patients with obstructive sleep apnea may have difficulty exhaling against positive pressure, hence limiting their acceptance of continuous positive airway pressure (CPAP). C-Flex is designed to improve comfort by reducing pressure in the mask during expiration proportionally to expiratory airflow (3 settings correspond to increasing pressure changes). When patients use CPAP, nasal resistance determines how much higher supraglottic pressure is than mask pressure. We hypothesized that increased nasal resistance results in increased expiratory supraglottic pressure swings that could be mitigated by the effects of C-Flex on mask pressure.

Design: Cohort study.

Setting: Sleep center.

Participants: Seventeen patients with obstructive sleep apnea/hypopnea syndrome and a mechanical model of the upper airway.

Interventions: In patients on fixed CPAP, CPAP with different C-Flex levels was applied multiple times during the night. In the model, 2 different respiratory patterns and resistances were tested.

Measurements and Results: Airflow, expiratory mask, and supraglottic pressures were measured on CPAP and on C-Flex. Swings in pressure during expiration were determined. On CPAP, higher nasal resistance produced greater expiratory pressure swings in the supraglottis in the patients and in the model, as expected. C-Flex 3 produced expiratory drops in mask pressure (range -0.03 to -2.49 cm H₂O) but mitigated the expiratory pressure rise in the supraglottis only during a sinusoidal respiratory pattern in the model.

Conclusions: Expiratory changes in mask pressure induced by C-Flex did not uniformly transmit to the supraglottis in either patients with obstructive sleep apnea on CPAP or in a mechanical model of the upper airway with fixed resistance. Data suggest that the observed lack of expiratory drop in supraglottic pressure swings is related to dynamics of the C-Flex algorithm.

Keywords: Upper airway resistance, nasal resistance, obstructive sleep apnea, fixed CPAP, flexible CPAP, CPAP compliance

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INTRODUCTION

Continuous positive airway pressure (CPAP) is the primary treatment for obstructive sleep apnea/hypopnea syndrome (OSAHS).^{1,2} CPAP use normalizes breathing, improves sleep architecture,³ enhances daily function,^{4,5} and reduces the number and severity of cardiovascular events.⁶⁻⁸ Despite the efficacy of CPAP, studies defining adherence as use for at least 4 hours per night have reported that 29% to 83% of patients did not adhere to CPAP therapy.^{9,10} Although multiple factors may contribute to CPAP intolerance, including mask fit, humidity, excessive mask leak, claustrophobia, and nasal symptoms,¹¹ pressure intolerance is a frequent complaint.⁹ In 2 studies,^{12,13} 29% and 18% of patients reported “difficulty exhaling” during CPAP treatment. Several small studies have also suggested that initial rejection of CPAP correlates with increased nasal resistance.¹⁴⁻¹⁶ Nasal resistance may contribute to CPAP intolerance through several mechanisms, including alterations in the route of breathing,^{17,18} the need for high CPAP pressure, and increased leak.¹⁹ During expiration, nasal resistance causes the pressure experienced by the patient to be higher than the prescribed

CPAP. This is because the resistance interacts with expiratory flow to produce a backpressure that adds to the CPAP (mask pressure), and this may contribute to discomfort.

Multiple technologic strategies have been proposed to improve CPAP adherence (including continuous automatic titration and bilevel therapy), but there is little evidence that these strategies significantly improve patient adherence.²⁰⁻²³ A recently introduced approach, C-Flex (Respironics; Murrysville, PA), is designed to improve comfort by modifying pressure in the mask during CPAP only during expiratory flow (in contrast with bilevel therapy, which maintains a low expiratory pressure throughout expiration). Although it is possible that any increased comfort (and consequent effect on compliance) achieved through reducing expiratory pressure may be achieved by reducing the pressure affecting the nose, it seems more likely that improved comfort would arise from reduction of **excessive** supraglottic pressure swings (i.e., that the drop in mask pressure would offset the expiratory rise in pharyngeal pressure above the prescribed CPAP).

Prospective randomized studies have demonstrated that C-Flex is not inferior to conventional fixed CPAP,^{24,30} but increased adherence rates have not been uniformly demonstrated. Some studies have shown that C-Flex reduces discomfort^{26,28} and improves satisfaction²⁵ and compliance,^{27,31} but larger randomized studies^{29,30} have shown no difference in compliance between CPAP and C-Flex.

During well-titrated CPAP, collapsibility of the upper airway (UA) is abolished. In this condition, total UA resistance is dic-

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tated by nasal resistance, which, at constant CPAP, necessarily produces flow-related effects on supraglottic pressure. During expiration, this supraglottic pressure (pressure from the mask plus any pressure resulting from the expiratory flow) determines the expiratory work of breathing and could contribute to patient symptoms and CPAP intolerance. The purpose of the present study was to examine whether C-Flex decreases supraglottic pressure swings during expiration, providing a mechanism for improved comfort. This study did not examine comfort, treatment adherence, or clinical outcomes per se; our goal was to define the underlying physiology and effects of C-Flex to better address the role it has in the clinical setting (e.g., defining its relevance to patients with high nasal resistance). Specifically, we examined the expiratory pressure profile at the mask and in the upper airway at the supraglottis in asleep patients while they were on CPAP with and without C-Flex. We also examined whether expiratory supraglottic pressure swings could be mitigated with the application of C-Flex. In addition to testing the application of C-Flex in patients with OSAHS, we also used a mechanical model of the UA to control respiratory flow and pattern and to eliminate reflex changes seen in patients

METHODS

Patients with OSAHS

Twenty-two adults presenting for evaluation of OSAHS with complaints of snoring and excessive daytime sleepiness were recruited for this study. Demographic and clinical variables were documented. Patients were excluded if they had a medically unstable condition (i.e., recent myocardial infarction, congestive heart failure) or if they were unable to sleep with CPAP.

All patients underwent full nocturnal polysomnography to confirm the diagnosis of OSAHS, and the polysomnogram was performed as per American Academy of Sleep Medicine recommended clinical guidelines.^{32,33} If CPAP treatment was clinically indicated, the patients were referred for in-laboratory CPAP-titration polysomnography.³⁴ In addition to the usual measurements of mask flow and mask pressure, supraglottic pressure measurements were also obtained during optimal fixed CPAP and at the same CPAP level with expiratory pressure reduction (C-Flex). C-Flex produces a constant inhalation pressure but reduces airway pressure during exhalation in proportion to the patient's expiratory airflow (thus, a drop in pressure occurs primarily during early expiration). C-Flex allows for 3 settings, C-Flex 1, C-Flex 2, C-Flex 3, which correspond to an increasing proportionality constant between expiratory flow and pressure reduction.

During the CPAP-titration polysomnography, pressure was directly measured at the mask using a pressure transducer (Ultima Dual Airflow Pressure Sensor™, Braebon 0585, Ontario, Canada). Airflow was recorded from the output of a Respirationics BiPAP Auto M Series device in CPAP mode. CPAP was titrated manually during the first hour of the study to a level that eliminated all sleep-disordered breathing events, including obstructive apneas and hypopneas and runs of inspiratory flow limitation. The optimal pressure was defined as the minimum pressure at which flow limitation disappeared. This pressure was determined by performing step-down measures, i.e., dropping the pressure every 2 minutes by 1 cm H₂O until indications

of inspiratory flow limitation occurred. The pressure prior to the appearance of flow limitation established the minimum therapeutic pressure.

In addition to standard monitoring, supraglottic pressure was obtained using a pressure transducer-tipped catheter (Millar MPC 500, Millar Instruments, Houston, TX). The patient's nose was anesthetized using atomized lidocaine 5% and lidocaine 2% jelly for the throat. The Millar catheter was introduced transnasally, and the tip of the catheter was placed just below the uvula. The catheter position was confirmed visually through the mouth. The catheter was taped to the nose to secure its position throughout the study. The nasal CPAP mask was then applied, and leak at the exit site of the catheter was minimized. The output of the Millar catheter was amplified and recorded at 64 Hz. To verify that the supraglottic catheter tip was placed just below the collapsible segment of the UA, the tracings from the supraglottic and CPAP inspiratory pressures after the patient fell asleep were inspected during a brief "step-down" of CPAP pressure. Correct positioning of the catheter tip required that the delta pressure between the mask and the supraglottic area increased substantially during inspiration and that evidence of inspiratory flow limitation appeared simultaneously. If this increase in delta pressure was not observed while the CPAP was reduced, the technician assumed that the catheter position was too high and advanced the catheter.

Interventions were performed after 5 minutes of stable stage N2 sleep with the patient on optimal CPAP. The data were discarded if an arousal occurred. Three different levels of C-Flex were applied cyclically multiple times throughout the night. The order of application of C-Flex level was not randomized. Each level was maintained for 1 minute, and fixed CPAP was restored at the end of the sequence, which was repeated at least twice, up to 10 times, across the night. Changes in pressure were accomplished with a single machine while patients were asleep, and, thus, patients were effectively blinded to the intervention.

Subjects signed a consent form approved by the Institutional Review Board of the New York University School of Medicine.

Mechanical Model of the Upper Airway

To create a bench test for some of our observations in patients, we designed a mechanical model of the upper airway in patients on CPAP (i.e., without a collapsible airway) (Figure 1). This model consisted of a rigid resistive tube, the resistance of which could be varied by changing the aperture size. A pure sinusoidal respiratory pattern was generated using a mechanical pump (Respiration Pump 607, Harvard Apparatus Co, INC. Dover, MA). In a separate data collection, a healthy volunteer breathing through the system generated a "normal" breathing pattern (exponential expiration with pause). Airflow was measured from the output of a Respirationics BiPAP Auto M Series device in CPAP mode. Simulated mask pressure was measured with a pressure transducer (Ultima Dual Airflow Pressure Sensor). Simulated supraglottic pressure was obtained using the Millar catheter. Measurements were obtained using these 2 respiratory patterns at 2 respiratory rates and 2 tidal volumes. All measurements were performed with 2 different resistances on CPAP and on C-Flex settings. Three different levels of C-Flex were applied and maintained for 1 minute each, and fixed CPAP was restored at the end of the sequence, which was repeated.

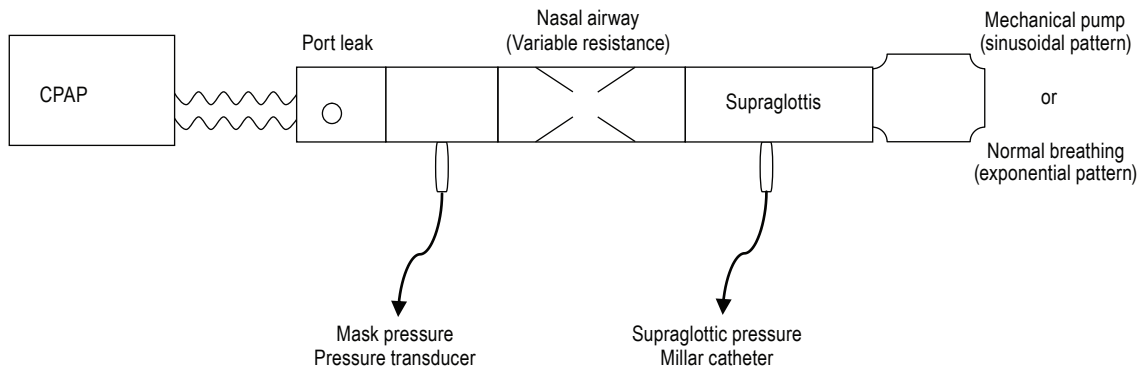


Figure 1—Mechanical model of the upper airway. The model consists of a rigid resistive tube with a variable “upstream” upper airway resistance controlled by changing the aperture size to mimic a patient using nasal continuous positive airway pressure (CPAP). A rigid tube was used to model the upper airway because dynamic collapse does not occur in patients on CPAP. The pressure taps are placed within the model to obtain measurements that simulate nasal and supraglottic pressures in a patient. Patterns of breathing were applied by a mechanical pump (sinusoidal) or a healthy volunteer breathing on a mouthpiece (“normal” pattern).

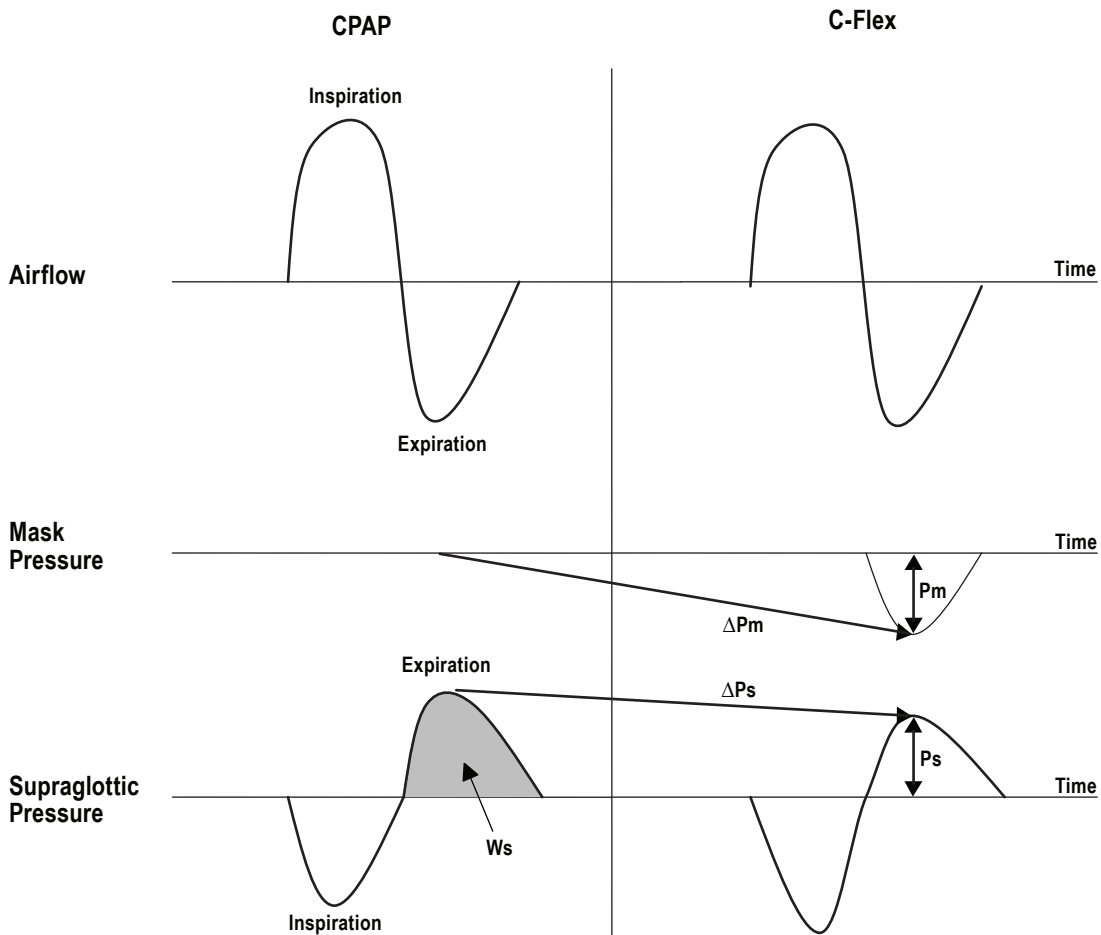


Figure 2—This drawing shows data collected and variables analyzed for a single breath. The left panel shows continuous positive airway pressure (CPAP) and the right shows C-Flex 3. The top tracing shows airflow (inspiration up). The middle tracing is pressure at the mask, and the bottom tracing is supraglottic pressure (inspiration down). P_m refers to the expiratory pressure swing in the mask; P_s , expiratory pressure swing in the supraglottis; ΔP_m , change in expiratory mask pressure swings (C-Flex 3 minus CPAP); ΔP_s , change in expiratory pressure swings in the supraglottis (C-Flex 3 minus CPAP); W_s , estimated expiratory work by calculating the integrated supraglottic pressure during expiration (grey area).

Analysis

Figure 2 shows a drawing of airflow, mask pressure, and supraglottic pressure signals and the derived variables. Respira-

tory variables were analyzed only during the expiratory phase. We assessed values of variables on CPAP and on different C-Flex settings. Mask pressure (P_m in Figure 2) is the expiratory

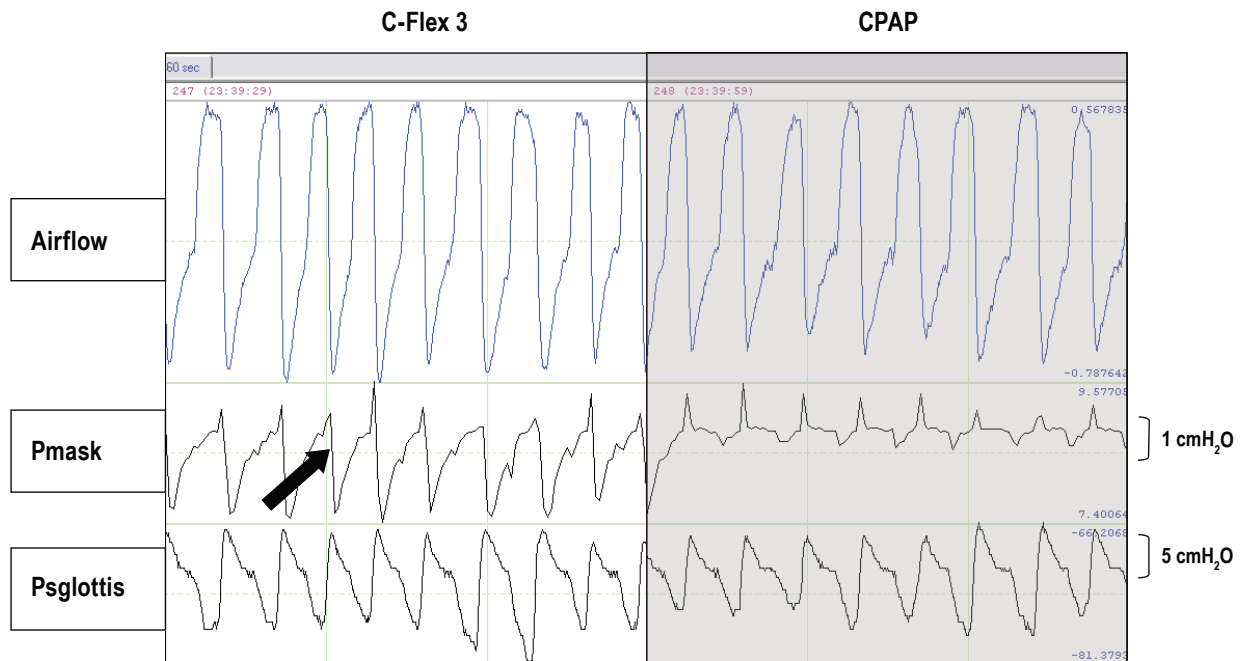


Figure 3—The raw tracing data of airflow, mask pressure (Pmask), and supraglottic pressure (Psglottis) from a patient with obstructive sleep apnea-hypopnea syndrome on C-Flex 3 and continuous positive airway pressure. The arrow shows the reduction of mask pressure during expiration with the application of C-Flex 3.

pressure swing in the mask (the difference between mask pressure at peak expiratory airflow and mask pressure at the end of expiration, which is the set CPAP). Supraglottic pressure (P_s) is the expiratory pressure swing in the supraglottis (the difference between the supraglottic pressure at peak expiratory airflow and the supraglottic pressure at the end of expiration). Delta P_m (ΔP_m) is the change in mask-pressure swings with application of C-Flex (P_m on C-Flex minus P_m on CPAP). Delta P_s (ΔP_s) is the change in supraglottic pressure swings with application of C-Flex (P_s on C-Flex minus P_s on CPAP). We calculated the integrated supraglottic pressure during expiration (W_s) as a surrogate for expiratory work. The UA resistance was calculated as the difference between mask pressure and supraglottic pressure at peak airflow divided by peak airflow.

In patients (during stage N2 sleep and in the same position) and in the UA model, we identified 2 separate periods suitable for data collection during which stable respiration was present. In each of these periods, data from 3 consecutive breaths were averaged to obtain the value for each variable on C-Flex 1, C-Flex 2, C-Flex 3, and fixed CPAP. The average value from 2 segments is reported as a single value for each variable on C-Flex 1, C-Flex 2, C-Flex 3, and fixed CPAP. Analysis of the supraglottic pressure signal was done without hiding the mask pressure signal, and the investigator was, thus, not blinded as to the presence of C-Flex.

Statistical analysis was performed using SPSS for Windows (version 17; SPSS, Chicago, IL). An independent samples t-test was used for comparisons between low and high resistance. Comparisons of ΔP_m and ΔP_s were made using paired-samples t-test comparing CPAP with C-Flex 3. Significance was assumed at a P value of less than 0.05. Values are shown as mean \pm SD.

RESULTS

Patients with OSAHS

Of the 22 patients with OSAHS who were recruited, 17 (13 men/4 women) completed the study: the remaining potential subjects were excluded due to insufficient sleep ($n = 2$), excessive mask leak ($n = 2$), and poor signal quality from the supraglottic catheter ($n = 1$). The mean age was 49.2 ± 11.1 years, mean body mass index, 35.1 ± 9.8 kg/m²; the mean apnea-hypopnea index, 61.2 ± 35.1 events/h; the mean respiratory index disturbance 64.8 ± 35.1 events/h, mean Epworth Sleepiness Scale score, 12.7 ± 5.4 ; and the mean CPAP level, 10.11 ± 3.5 cm H₂O.

Figure 3 shows raw-tracing data of airflow, mask pressure, and supraglottic pressure from 1 patient with OSAHS. Swings in the expiratory mask pressure in the patients during CPAP were near 0 ($P_m = +0.09 \pm 0.08$ cm H₂O) and, as expected, swings in the supraglottic expiratory pressure did occur ($P_s = +1.87 \pm 1.30$ cm H₂O). During C-Flex 3, all patients developed expiratory mask pressure dips ($P_m = -1.13 \pm 0.48$ cm H₂O), and the drop of P_m was progressive as C-Flex went from setting 1 to setting 3 (Figure 4A). Concurrently, expiratory supraglottic pressure swings (P_s) were $+1.75 \pm 1.19$ cm H₂O (Figure 4B). Thus, unexpectedly, there was no significant reduction in supraglottic expiratory pressure swings during C-Flex, compared with the swings present in P_s during CPAP alone ($P = 0.46$). Figure 5A shows the effect of C-Flex compared with CPAP on P_m in the individual patients. The transmission of the expiratory mask pressure swings to the supraglottis did not occur in 15 of the 17 patients (e.g., ΔP_m was -1.23 ± 0.53 cm H₂O and ΔP_s was -0.06 ± 0.47 cm H₂O, $P = 0.000$, see Figure 5B). This behavior was in contrast to the expectation that C-Flex would reduce or abolish changes in expiratory supraglottic pressures.

When patients were using CPAP during sleep, no differences occurred between the mean inspiratory and mean expiratory instantaneous UA resistance ($0.12 \pm 0.08 \text{ cm H}_2\text{O}\cdot\text{L}^{-1}\cdot\text{min}^{-1}$ vs $0.10 \pm 0.09 \text{ cm H}_2\text{O}\cdot\text{L}^{-1}\cdot\text{min}^{-1}$, $P = 0.11$). Table 1 examines the role of expiratory UA (upstream) resistance on our findings by separating our patients whose expiratory UA resistance was less than ($n = 12$) and greater than ($n = 5$) $0.1 \text{ cm H}_2\text{O}\cdot\text{L}^{-1}\cdot\text{min}^{-1}$, in accord with what has been shown in the literature on nasal resistance.³⁵⁻³⁷ Patients with low UA resistance during CPAP use (constant mask pressure) showed expiratory pressure swings at the supraglottis (P_s) of $+1.15 \pm 0.45 \text{ cm H}_2\text{O}$. As expected, P_s was significantly greater ($P = 0.001$) in patients with high levels of UA resistance ($+3.59 \pm 0.99 \text{ cm H}_2\text{O}$). On C-Flex 3, there were no discernable differences between groups for ΔP_m and ΔP_s .

To examine this unexpected lack of change in supraglottic pressure—despite a drop in expiratory pressure at the mask—we used a mechanical model in which the pattern of airflow could be controlled.

Mechanical Model of the Upper Airway

Sinusoidal respiratory pattern

When we implemented our mechanical model of the upper airway with a sinusoidal respiratory pattern and a *low* simulated UA resistance during CPAP (constant mask pressure), expiratory pressure swings at the simulated supraglottis (P_s) were $+1.94 \pm 1.47 \text{ cm H}_2\text{O}$. As expected, with a *high* simulated UA resistance, P_s increased to $+4.40 \pm 3.03 \text{ cm H}_2\text{O}$.

During the highest level of C-Flex (C-Flex 3), mask pressure developed expiratory dips and P_m was $-1.45 \pm 0.74 \text{ cm H}_2\text{O}$ on low simulated UA resistance and $-1.57 \pm 0.66 \text{ cm H}_2\text{O}$ on high simulated UA resistance. Concurrently, expiratory P_s was $+0.51 \pm 1.11 \text{ cm H}_2\text{O}$ on low simulated UA resistance and $+2.87 \pm 2.41 \text{ cm H}_2\text{O}$ on high simulated UA resistance.

Table 2 shows the effect of C-Flex compared with CPAP on P_m and P_s in our mechanical-model data. The data across a range of imposed tidal volumes and frequencies are grouped according to whether there was a low or high simulated upstream “UA” resistance. The change in P_s (ΔP_s) when going from CPAP to C-Flex 3 was similar to the change in P_m (ΔP_m) (e.g., there was no statistically significant difference in the magnitude of the swings between P_s and P_m). Furthermore, in the model, expiratory pressure swings were transmitted similarly from mask to supraglottis for all patterns of breathing and for low and high UA resistance.

Exponential respiratory pattern

When a healthy volunteer breathing on the upper airway model produced a nonsinusoidal (normal) respiratory pattern with a rapid peak in expiratory airflow followed by an exponential decay of flow, *low* simulated UA resistance during CPAP (constant mask pressure) produced expiratory pressure swings at the supraglottis (P_s) of $+4.09 \pm 2.74 \text{ cm H}_2\text{O}$. Again, as expected, high simulated UA resistance increased P_s to $+6.61 \pm 4.86 \text{ cm H}_2\text{O}$.

During the highest level of C-Flex (C-Flex 3), mask pressure developed expiratory dips and P_m was $-2.61 \pm 0.62 \text{ cm H}_2\text{O}$ on low simulated UA resistance and $-2.35 \pm 0.70 \text{ cm H}_2\text{O}$ on high simulated UA resistance. Concurrently, expiratory supraglot-

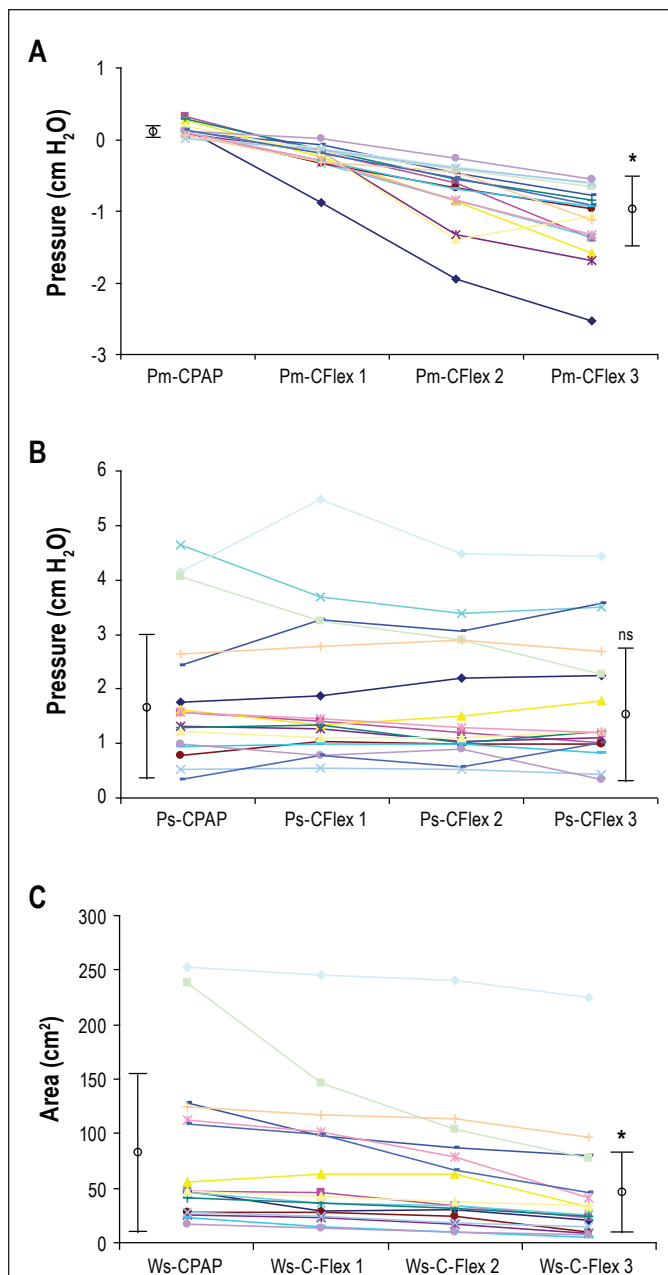


Figure 4—Data from patients with obstructive sleep apnea-hypopnea syndrome—the effect of C-Flex compared with continuous positive airway pressure (CPAP) on mask pressure swings (P_m), supraglottic pressure swings (P_s), and the estimated expiratory work (W_s). Each line represents a patient ($n = 17$) with lines connecting the magnitude of the expiratory pressure swing within the mask when the patient was using CPAP to the expiratory pressure swing within the mask when the patient was using C-Flex 3. **(A)** All patients developed expiratory dips, and the P_m showed progressive reduction on C-Flex 1, C-Flex 2, and C-Flex 3 compared with CPAP. The mean \pm SD values of the CPAP and C-Flex 3 are shown, and the * indicates a significant difference in the mean ($P < 0.0001$). **(B)** Patients did not show a reduction in expiratory supraglottic pressure swings (P_s) with the application of various levels of C-Flex. The mean \pm SD value of the CPAP and C-Flex 3 are shown, and ns indicates no significant difference in the means. **(C)** Patients showed a variable reduction of the integrated expiratory pressure in the supraglottis with C-Flex. This reduction may be most evident when comparing CPAP with the highest level of C-Flex 3. The mean \pm SD value of the CPAP and C-Flex 3 are shown, and the * indicates a significant difference in the mean ($P < 0.0001$).

Table 1—Expiratory mask and supraglottic pressure swings and effect of C-Flex compared to CPAP in OSAHS patients

OSAHS Patients	Low UA resistance (n = 12) (< 0.1 cm H ₂ O/L/min)		High UA resistance (n = 5) (> 0.1 cm H ₂ O/L/min)	
	CPAP	C-Flex 3	CPAP	C-Flex 3
Pm (cm H ₂ O)	0.11 ± 0.09	-1.21 ± 0.53	0.03 ± 0.02	-0.93 ± 0.31
Ps (cm H ₂ O)	+1.15 ± 0.45	+1.11 ± 0.52	+3.59 ± 0.99	+3.29 ± 0.84
ΔPm (cm H ₂ O)	-1.32 ± 0.55		-0.96 ± 0.31	
ΔPs (cm H ₂ O)	-0.04 ± 0.39		-0.29 ± 1.18	

Values are means ± standard deviation. UA, upper airway; CPAP, continuous positive airway pressure; C-Flex, reduction of expiratory pressure during CPAP; Pm, expiratory pressure swing in the mask; Ps, expiratory pressure swing in the supraglottis; ΔPm, change in mask pressure swings (C-Flex 3 minus CPAP); ΔPs, change in supraglottic pressure swings (C-Flex 3 minus CPAP).

tic pressure swings (Ps) were $+3.30 \pm 2.01$ cm H₂O on low simulated UA resistance and $+6.42 \pm 4.60$ cm H₂O on high simulated UA resistance.

Table 3 shows the effect of C-Flex compared with CPAP on mask and supraglottic pressure swings in the model data. The data across a range of imposed tidal volumes and frequencies are grouped according to whether there was a low or high simulated upstream “UA” resistance. In contrast with the findings during sinusoidal breathing, ΔPs was lower than the ΔPm ($P = 0.024$ for low simulated UA resistance and $P = 0.003$ for high simulated UA resistance). The lack of transmission of pressure swings from mask to supraglottis was most evident during the simulated high UA resistance.

Figure 6 combines the data in Tables 2 and 3 to contrast the effect of sinusoidal (Figure 6A) and “normal” nonsinusoidal (Figure 6B) breathing patterns on ΔPm and ΔPs in the model. Whereas there is a consistent transmission of mask pressure swings to the supraglottis in sinusoidal breathing patterns, mask pressure swings were NOT transmitted to the supraglottis during “normal” nonsinusoidal breathing (e.g., ΔPm was significantly more negative than ΔPs [$p = 0.024$ for low simulated UA resistance and $P = 0.003$ for high simulated UA resistance]).

Analysis of Expiratory Pressure-Time Curve

In addition to the analysis of the effect of C-Flex on expiratory peak pressures at the supraglottis, we also integrated the pressure-time curve as an estimate of expiratory work in patient and model data. This area measurement was used to re-evaluate the effectiveness of application of C-Flex to the UA of patients with OSAHS and our UA model (Figures 4C, 7). In Figure 7, for each condition (low and high resistance, sinusoidal and nonsinusoidal model data and patient data) the percentage change from CPAP to C-Flex 3 is shown for supraglottic expiratory pressure swings and expiratory area. We defined a change of 100% from the CPAP to C-Flex 3 value as complete reversal of the expiratory pressure swing in the supraglottis. In the UA model when UA resistance was low, application of C-Flex 3 produced complete reversal of expiratory Ps with sinusoidal breathing but produced a partial reversal with “normal” breath shape. Patients with OSAHS behaved similarly to the model data with “normal” breath and did not show much reversal of the expiratory pattern for Ps or Ws. When UA resistance was high, application of C-Flex 3 produced incomplete reversal of expiratory Ps and Ws in all cases for the model and patients. Thus, application of C-Flex reduced the integrated expiratory pressure in the supraglottis but not the peak (Figure 4C). This indicates that mask pressure is transmitted to the supraglottis but the transmission is not fast enough to reduce peak Ps. However, it does reduce the integrated pressure and may reduce expiratory work.

DISCUSSION

Our data show that, when mask pressure is constant during CPAP use, significant pressure swings occur in the supraglottis during expiration. The essential new finding of this study is

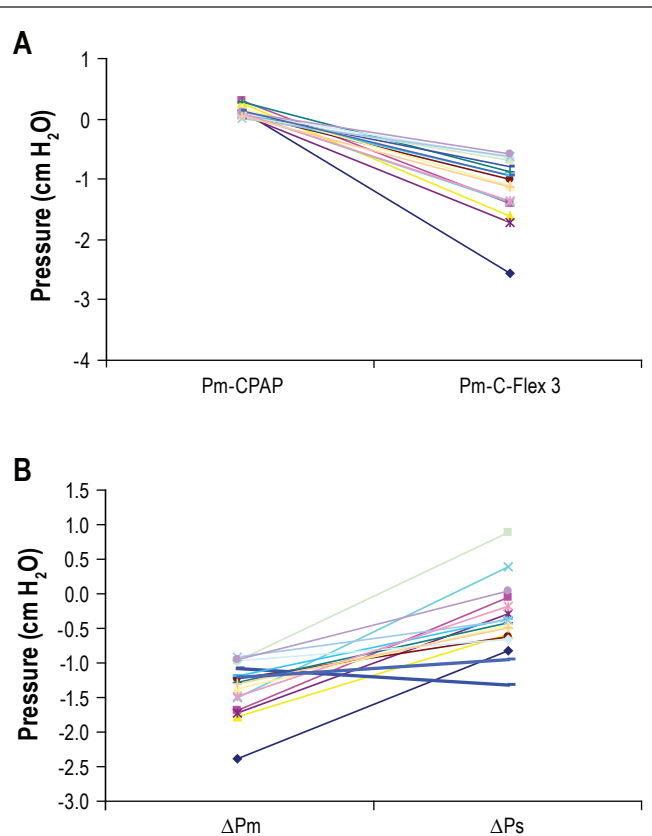


Figure 5—(A) Patients with obstructive sleep apnea-hypopnea syndrome—the effect of C-Flex compared with the effect of continuous positive airway pressure (CPAP) on mask pressure swings (Pm). Each line represents a patient (n = 17) with lines connecting the magnitude of expiratory pressure swing within the mask when the patient was using CPAP to the expiratory pressure swing within the mask when the patient was using C-Flex 3. All patients developed expiratory dips, and Pm showed reduction when patients were using C-Flex 3, compared with CPAP. (B) Patients with obstructive sleep apnea-hypopnea syndrome—the change in expiratory pressure swings with C-Flex 3. Each line represents a patient with lines connecting the change of expiratory mask pressure (Pm) between continuous positive airway pressure and C-Flex 3 and the change in expiratory supraglottic pressure (Ps). There was no transmission of the mask pressure swings to the supraglottis in 15 of the 17 patients (e.g., change in Pm [ΔPm] was more negative than change in Ps [ΔPs]). The 2 thick lines represent the 2 patients with a parallel drop in Pm and ΔPs.

Table 2—Effect of C-Flex compared with CPAP on mask and supraglottic expiratory pressure swings in the mechanical model with sinusoidal breathing

Upper Airway Model	Change (C-Flex 3 minus CPAP)	
	ΔP_m (cm H ₂ O)	ΔP_s (cm H ₂ O)
Sinusoidal respiratory pattern		
Low upper airway resistance (0.028 ± 0.018 cm H ₂ O/L/min)		
RR 10 bpm, TV 450 ml	-0.80	-0.81
RR 16 bpm, TV 450 ml	-1.34	-1.25
RR 24 bpm, TV 450 ml	-1.26	-1.37
RR 12 bpm, TV 800 ml	-1.25	-1.44
RR 24 bpm, TV 800 ml	-2.5	-2.25
Total group	-1.43 ± 0.64	-1.42 ± 0.52
High upper airway resistance (0.059 ± 0.022 cm H ₂ O/L/min)		
RR 12 bpm, TV 450 ml	-0.89	-0.80
RR 16 bpm, TV 450 ml	-1.22	-1.02
RR 24 bpm, TV 450 ml	-1.35	-1.60
RR 12 bpm, TV 800 ml	-1.95	-2.04
RR 24 bpm, TV 800 ml	-2.13	-2.29
Total group	-1.51 ± 0.52	-1.55 ± 0.64

Values for total group are means ± standard deviation. RR, respiratory rate; TV, tidal volume; bpm, breath per minute; ΔP_m , change in mask pressure swings (C-Flex 3 minus CPAP); ΔP_s , change in supraglottic pressure swings (C-Flex 3 minus CPAP).

Table 3—Effect of C-Flex compared to CPAP on mask and supraglottic expiratory pressure swings in the mechanical model with exponential breathing

Upper Airway Model	Change (C-Flex 3 minus CPAP)	
	ΔP_m (cm H ₂ O)	ΔP_s (cm H ₂ O)
Exponential respiratory pattern		
Low upper airway resistance (0.040 ± 0.014 cm H ₂ O/L/min)		
RR 14 bpm, TV~500 ml	-2.45	-0.37
RR 28 bpm, TV~500 ml	-2.21	-0.38
RR 16 bpm, TV~(2× baseline) ml	-2.80	-1.63
Total group	-2.48 ± 0.3	-0.79 ± 0.72
High upper airway resistance (0.075 ± 0.004 cm H ₂ O/L/min)		
RR 16 bpm, TV~500 ml	-1.69	0
RR 26 bpm, TV~500 ml	-2.11	-0.09
RR 16 bpm, TV~(2× baseline) ml	-2.34	-0.47
Total group	-2.05 ± 0.33	-0.19 ± 0.25

Values for total group are means ± standard deviation. RR, respiratory rate; TV, tidal volume; bpm, breath per minute; ΔP_m , change in mask pressure swings (C-Flex 3 minus CPAP); ΔP_s , change in supraglottic pressure swings (C-Flex 3 minus CPAP).

that imposed expiratory changes in mask pressure produced by C-Flex did not uniformly transmit to the supraglottis in either patients with OSAHS on CPAP or in a mechanical model of the upper airway with a fixed resistance. Our model data comparing breaths with a sinusoidal shape to breaths with an exponential expiratory decay (“normal”) of airflow suggest to us that the observed lack of expiratory drop in supraglottic pressure swings is related to dynamics of the C-Flex algorithm that con-

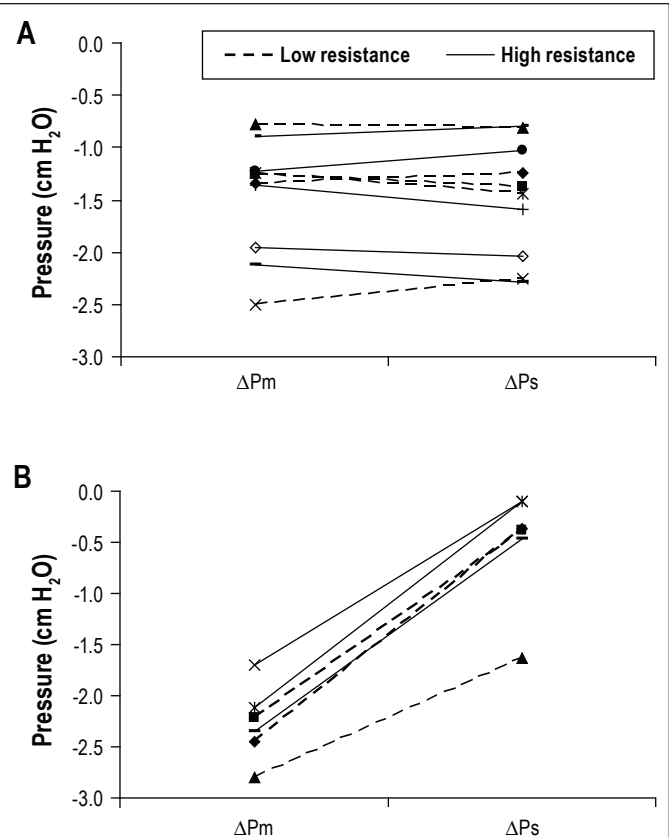
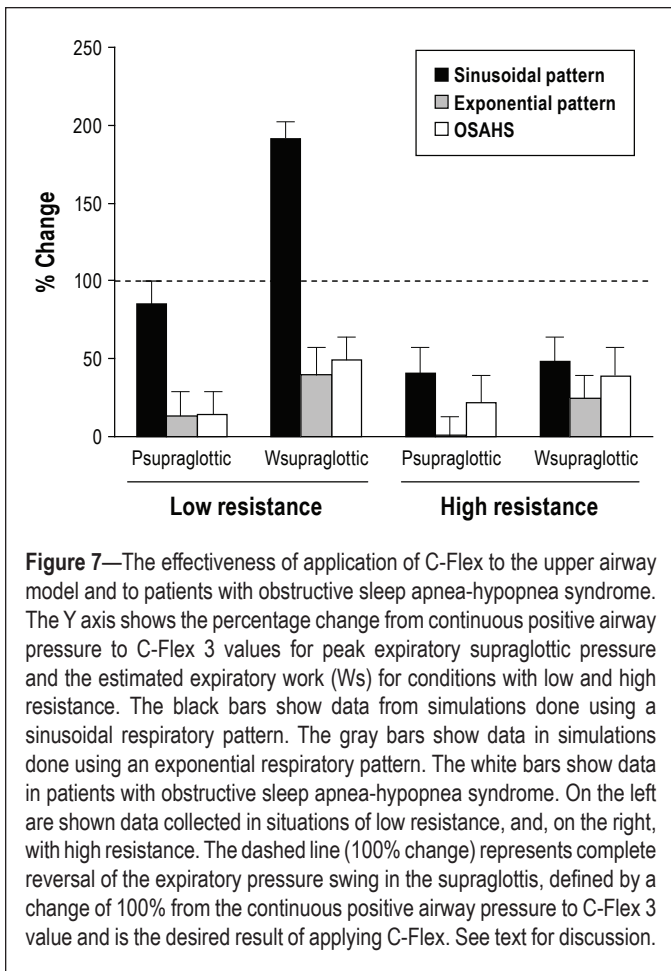


Figure 6—Upper airway model—change in expiratory pressure swings with C-Flex 3. Each line represents a different tidal volume or frequency. Dashed lines are simulations with low upper airway resistance, and the solid lines are simulations with high upper airway resistance connecting the change of expiratory mask pressure between continuous positive airway pressure and C-Flex 3 and the change of expiratory supraglottic pressure. **(A)** Sinusoidal respiratory pattern. There is a consistent transmission of expiratory mask pressure swings to the supraglottis (eg ΔP_m is similar to ΔP_s). **(B)** “Normal” (exponential expiration) respiratory pattern. Expiratory mask pressure swings were not transmitted to the supraglottis (eg ΔP_m was significantly more negative than ΔP_s).

trols mask pressure rather than to intrinsic properties of the upper airway.

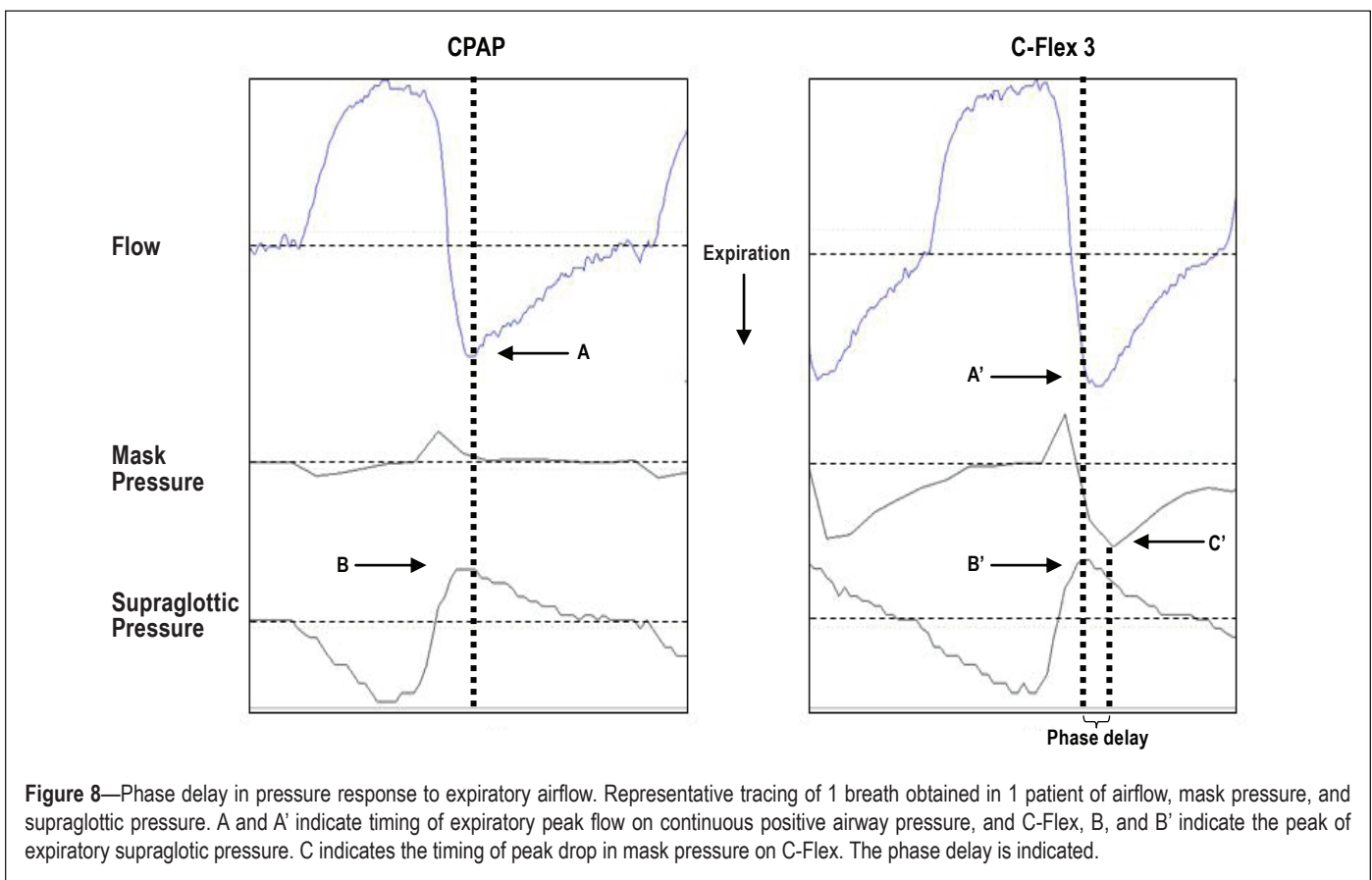
In our mechanical model of the UA on CPAP, we found that, during expiration, as expected, high nasal resistance (upstream) produced greater pressure swings in the supraglottis than low nasal resistance. Only with a sinusoidal respiratory pattern did the expiratory pressure drop in the mask produced by C-Flex successfully mitigate the expiratory rise in pressure seen in the supraglottis, which is the intended purpose we attribute to C-Flex. In contrast, when tested in our model with breaths having the more physiologically typical exponential respiratory pattern, application of C-Flex caused little reduction of supraglottic pressure swings during expiration, despite a similar drop of mask pressure. Similarly, in the patients with OSAHS, application of C-Flex produced a drop in expiratory mask pressure in all patients; however, most patients did not demonstrate the expected fall in supraglottic pressures swings.

One explanation of our primary finding, i.e., that the C-Flex algorithm may not work as well with nonsinusoidal patterns of breathing as with pure sinusoidal expiration, may be related to



the occurrence of rapid changes in flow during early expiration with an exponential pattern. Inspection of the pressure and flow tracings suggests that a phase delay in the pressure response to expiratory flow was present. Figure 8 shows a typical example from one patient. The drop in mask pressure occurs well after the initiation of the rise of supraglottic pressure during early expiration. This phase lag between flow and mask pressure, and the persistence of supraglottic pressure swings on C-Flex, was seen in all of the patients (mean phase lag 0.31 ± 0.06 sec; range, 0.19-0.42 sec) and also during the exponential expiratory pattern in the model data (mean phase lag 0.28 ± 0.10 sec; range, 0.15-0.41 sec). To further understand this phenomenon, we attempted to find a relationship between the presence of a phase lag between peak expiratory flow and peak mask expiratory pressure drop and respiratory frequency but were not able to do so within the range of respiratory patterns recorded. Thus, we cannot say with certainty whether the failure of C-Flex to abolish the expiratory supraglottic pressure swings was due to only a rapid change in expiratory flow or to some other aspect of nonsinusoidal breathing.

An alternate explanation of our findings of a lack of change in expiratory supraglottic pressure despite a drop in mask pressure during C-Flex in the patients with OSAHS is that there was unexplained development of expiratory flow limitation in the upper airway that occurred only in association with C-Flex. We are aware of no neural or mechanical reason for such a behavior of the relatively rigid nasal airway on CPAP. Specifically, the behavior of the UA while the patient is on CPAP should be relatively invariant because the collapsible segment of the UA that is usually responsible for changes in airway resistance during



sleep is being “splinted” throughout the respiratory cycle above optimal CPAP.

Although C-Flex did not show much effect on peak expiratory supraglottic pressure swings, we did record some reduction in the W_s , (our estimate of expiratory work). However, we achieved only a partial reversal of the “expiratory phenomenon” with the maximum available settings of C-Flex (Figure 7). We have no way of assessing whether comfort, or the perception of discomfort by a patient during expiration, is affected more by mitigating the peak pressure or by mitigating work of exhalation; this may need to be tested directly.

One limitation of our study is that we did not recruit patients based on nasal resistance and, thus, did not have a large number of patients with high nasal resistance. We could have attempted to increase the number of patients in this study who had high nasal resistance by recruiting based on awake subjects’ complaints of nasal symptoms or on the results of testing obtained during wake (such as with rhinomanometry or acoustic rhinometry) that showed a high nasal resistance. However, we have previously shown that awake noninvasive measures of nasal resistance are not predictive of nasal resistance asleep.³⁸ Furthermore, despite a limited range in nasal resistances in the present data, we did show in the present dataset that, *on CPAP*, patients with high UA resistance had greater supraglottic pressure swings than did patients with low resistance.

A second possible limitation is that we did *not* specifically select patients who had reported intolerance to CPAP, and, in this study, we did not assess level of comfort. Thus, we cannot relate increased expiratory supraglottic pressure swings (or work) to perceived comfort on CPAP or an effect of C-Flex on reported comfort. However, this was not the objective of the present study. Furthermore, our patients were being studied during a first exposure to CPAP, during which they had multiple interventions (CPAP titration, trial with different settings of C-Flex), and these circumstances would have made collecting patients’ acute impressions of comfort difficult to interpret.

A final caveat exists in interpreting the results of these data: by design, we studied the effect of C-Flex-induced pressure drops at the mask on supraglottic pressure in patients only *during sleep*; “comfort” may be partially or wholly affected by the conditions *during wake*. The analysis reported here is based on measurements made during stage N2 sleep; in our current data set, we did not record much data when subjects were breathing in the wake state. In the limited wake periods available for analysis, we saw no trends toward a greater transmission of mask to supraglottic pressure swings while patients were on C-Flex.

In conclusion, we were not able to show that C-Flex reduces expiratory pressure swings in the supraglottis in patients with OSAHS on CPAP during sleep. Although C-Flex did succeed in reducing “supraglottic” pressure swings in our modeling studies using sinusoidal breathing, the magnitude of C-Flex mask-pressure reductions was not sufficient to eliminate expiratory supraglottic pressure swings at *any* setting for other patterns. These nonsinusoidal model data are similar to the data in patients. Our observations suggest that maximum potential physiologic impact of C-Flex on supraglottic pressure may not have been achieved by the present algorithm, and this may account for the recent data showing little effect of C-Flex use on overall CPAP compliance.^{29,30} Because there was surprisingly little physiologic

expiratory effect at the supraglottis of C-Flex during sleep with the present implementation of expiratory pressure modification by C-Flex, it is not possible to test the hypothesis that optimal mitigation of supraglottis expiratory pressure swings will improve patient comfort and compliance. However, if C-Flex does improve comfort, it is unlikely to do so by the mechanism of reducing the peak expiratory supraglottic pressure

ABBREVIATIONS

- CPAP, continuous positive airway pressure
- OSAHS, obstructive sleep apnea/hypopnea syndrome
- UA, upper airway
- Pm, mask pressure
- Ps, supraglottic pressure
- ΔP_m , delta mask pressure
- ΔP_s , delta supraglottic pressure
- W_s , integral of pressure \times expiratory time (surrogate for expiratory work)

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