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Air Leak during CPAP Titration as a Risk Factor for Central Apnea

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Objectives: Emergence of central sleep apnea has been described in the setting of continuous positive airway pressure (CPAP) initiation. The underlying mechanism is unclear; however, we postulate that air leak washing out anatomical dead space is a contributing factor.

Design: Data were obtained from 310 patients with obstructive sleep apnea (OSA) who underwent either split-night or full-night CPAP titration during January to July of 2009. The majority (n = 245) underwent titration with a nasal mask. Average total leak and maximum total leak were measured at therapeutic CPAP level. Unintentional leak was calculated by subtracting manufacturer-defined intentional leak from maximum leak.

Results: Subjects were divided into two groups: central apnea index (CAI) during titration < 5/hour and ≥ 5/hour. The groups were similar in terms of gender, age, BMI, and AHI. The CAI < 5 group had a median average leak of 45.5 L/min (IQR 20.8 L/min) versus 51.0 L/min (IQR 21.0 L/min) with CAI ≥ 5

(p = 0.056). Maximum leak was 59.5 L/min (IQR 27.0 L/min) with CAI < 5 and 75.0 L/min (IQR 27.8 L/min) with CAI ≥ 5 (p = 0.003). In the subset of subjects titrated using a nasal mask, median average leak was 42.0 L/min (IQR 17.0) in the CAI < 5 group and 50.0 L/min (IQR 16.8) in the CAI ≥ 5 group (p = 0.001). In the CAI < 5 group, median maximum leak was 57.0 L/min (IQR 23.0) versus 74.5 L/min (IQR 24.3) in the CAI ≥ 5 group (p < 0.001).

Conclusions: Leak during CPAP titration is associated with the development of acute central apnea; these data may have mechanistic and therapeutic implications for complex apnea.

Keywords: Sleep apnea, air leak, central apnea

Commentary: A commentary on this article appears in this issue on page 1193.

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Obstructive sleep apnea (OSA) is a common yet underdiagnosed and underappreciated disorder.¹ Once diagnosed, continuous positive airway pressure (CPAP) therapy is the treatment of choice. CPAP has been shown to be effective at reducing obstructive apnea when adequate pressure is applied. However, in a proportion of patients, initiation of CPAP treatment has been associated with the development of central apneas.^{2,3} Traditionally, central apnea has been observed in the setting of congestive heart failure,^{4,6} cerebrovascular disease,^{7,8} and high altitude.⁹ More recently, the recognition of CPAP-induced central apnea has led to considerable discussion.^{3,10,11} The terms “complex sleep apnea” and “treatment-emergent central apnea” have been used to describe the development of central apnea upon exposure to CPAP.^{3,10} From retrospective data of over 1200 patients with OSA initiated on CPAP, 6.5% were found to have treatment-emergent acute central apnea, with persistence after 8 weeks in only 1.5% of titrations.¹² Prior observational studies have also supported that for the majority of patients, the central apneas resolve with time.¹³ Patients who have a poor initial experience with CPAP may be reluctant to use CPAP in the long term; therefore, stabilization of breathing acutely may have benefits. On the other hand, expensive newer devices may be unnecessary if the breathing pattern is likely to stabilize spontaneously without any impact on clinical outcome.

BRIEF SUMMARY

Current Knowledge/Study Rationale: CPAP initiation has been associated with the emergence of central apneas. This study aims to determine the relationship, if any, between CPAP mask leak and central apneas.

Study Impact: The amount of leak during CPAP titration is associated with the emergence of central apneas. Further research is needed to elucidate the underlying mechanisms.

Several possible mechanisms are theorized to explain the development of central apneas with the initiation of CPAP therapy.^{14,15} First, pulmonary stretch receptors may inhibit ventilatory motor output, such that central apneas would be predicted to occur with high CPAP levels due to lung stretch.¹⁵ Second, CPAP serves to stabilize the upper airway, which would be predicted to increase controller gain in these patients.^{15,16} Chemoresponsiveness, defined as the body's ventilatory response to CO₂ plus the ability to respond to chemical stimuli (an open airway), would increase with CPAP-induced patency of the upper airway.¹⁷ Thus, central apnea may occur due to CPAP-induced hypocapnia.¹⁸ Third, and of particular importance in the current study, CPAP may reduce PaCO₂ by reducing the amount of dead space, particularly in patients who develop leak while on therapy.¹⁵ The CPAP mask and the upper airway are both sources of re-breathing, and the delivery of fresh gas from the CPAP machine may serve to wash out

these sources of re-breathing, therefore lowering PaCO₂ for any given minute ventilation. For example, in nasal CPAP treated patients with mouth leak, there may be a lowering of PaCO₂ due to washout of anatomical dead space in the upper airway.¹⁹ Thus, a number of potential mechanisms exist which could explain why these central apneas occur upon CPAP initiation.²⁰ Deciphering the underlying mechanisms has clinical importance as it may help inform the optimal intervention to reduce these events.

Based on the above logic, we sought to determine whether air leak was associated with the development of central apnea among patients undergoing CPAP titration. We performed a consecutive case series of patients with predominantly obstructive events undergoing CPAP titration to test the hypothesis that leak would be higher in those developing central apnea.

METHODS

Protocol

Data were obtained from adult patients with OSA undergoing either full-night diagnostic polysomnography followed by a separate attended titration, or split-night diagnostic/titration studies, at Sleep HealthCenters affiliated with Brigham and Women's Hospital in Boston, MA, during the time period of January to July of 2009. Patients were excluded if they were known to have one of the following medical conditions: lung disease including home oxygen use, congestive heart failure, valvular heart disease or cardiomyopathy, atrial fibrillation, implanted cardiac defibrillator or pacemaker. Use of oxygen during the sleep study and a total < 15 minutes of sleep time at optimal CPAP level were also grounds for exclusion.

Protocol approval was obtained through the Allendale Institutional Review Board (MR-0821-RFLW-BOS).

Sleep Studies

PSG consisted of electroencephalogram (C4-A1, C3-A2, O2-A1, O1-A2), bilateral electro-oculogram, bilateral chin and tibial electromyogram, electrocardiogram, airflow using thermistor and nasal pressure sensors, abdominal and thoracic respiratory excursion measured by piezo bands, pulse oximetry, and body position. Sleep studies were performed and scored by registered polysomnographic technologists according to published guidelines (blinded and naive to the goals of our study).^{21,22} Subjects were titrated using either oro-nasal cushion, nasal cushion, or nasal pillow masks as determined by technologist and subject preference.

An OmniLab multi-mode titration device (Respironics, Murrysville, PA, USA) was used for both the split and full-night CPAP titrations, which recorded a continuous estimation of total leak. The average total leak and the maximum total leak were measured at optimal CPAP level. Maximum leak was defined by non-transient maximal elevation with duration > 3 seconds. Any periods of time during which the CPAP mask was removed were excluded from data analysis. Intentional leak was for each type of mask used was defined according to manufacturer specifications. The amount of

excess leak was determined by subtracting intentional leak from total leak.

Additional Measured Variables

Variables obtained for each subject included gender, age, body mass index (BMI), and Epworth Sleepiness Scale (ESS) score. The presence or absence of known hypertension, diabetes mellitus, or ischemic heart disease was recorded.

Data Analysis

Statistical analysis was performed using SigmaStat Version 11 (Systat Software Inc., IL USA). Continuous data were analyzed for normality of distribution and homogeneity of variance; all outcome data were not normally distributed; therefore, between-group comparisons were made using Mann-Whitney tests. Categorical data were compared using χ^2 tests. All p-values are 2-sided, and were considered statistically significant at ≤ 0.05 .

RESULTS

Subjects

Data from 310 subjects with predominantly obstructive events during the diagnostic period were obtained. Of these, 240 titrations were performed with nasal CPAP masks (either cushion or pillow designs). Subjects were divided into 2 groups: those that had a central apnea index < 5 (n = 280) and $\geq 5/h$ (n = 30) during the titration period (at optimal CPAP level). The 2 groups were not significantly different in terms of age, BMI, ESS, gender, or the presence of hypertension, diabetes mellitus, or ischemic heart disease as detailed in **Table 1**. The groups were similar in terms of diagnostic AHI, sleep efficiency, and the % of REM sleep. The groups diverged when comparing the diagnostic CAI, the titration AHI, and titration sleep efficiency (see **Table 1**).

Leak Measurements and Analysis

When performing leak analysis for all 310 subjects, trends towards differences were found between the 2 groups with regards to the amount of average and peak leak measured (see **Table 2**). Subjects in the CAI < 5 group had an average leak of 45.5 L/min with an average unintentional leak of 19.0 L/min, whereas subjects in the CAI ≥ 5 group had an average leak of 51.0 L/min with an average unintentional leak of 24.5 L/min (p = 0.056 for average leak and p = 0.057 for average unintentional leak). Differences were also seen in peak leak amounts between the 2 groups with a peak and peak excess leak of 59.5 L/min and 34.0 L/min, respectively, with CAI < 5 and a peak and peak excess leak of 75.0 L/min and 52.5 L/min, respectively with CAI ≥ 5 with p values of 0.003 and 0.001 (peak and excess peak, respectively).

For the 240 subjects undergoing nasal CPAP titrations only, significant differences were found between the 2 groups in both average leak and peak leak measurements (**Table 3**). Average leak was 42.0 L/min with an average excess leak of 18.0 L/min in the CAI < 5 group and 50.0 L/min with an average excess leak of 25.5 L/min in the CAI ≥ 5 group (p = 0.001 and p = 0.005 for average leak and average excess leak, respectively). In the

Table 1—Clinical characteristics of subjects

	CAI < 5 events/hour N = 280	CAI ≥ 5 events/hour N = 30	p value
Titration using nasal masks	221 (79%)	24 (80%)	0.90
Age (years)	46.5 (18.5)	49.0 (15.2)	0.26
BMI (kg/m ²)	32.3 (10.9)	33.5 (12.0)	0.41
Epworth score (/24)	10.0 (7.0)	8.5 (6.5)	0.26
Female gender (number/%)	97 (35%)	13 (43%)	0.46
Presence of hypertension (number/%)	102 (37%)	13 (43%)	0.60
Presence of ischemic heart disease (number/%)	17 (6%)	0 (0%)	0.33
Presence of diabetes mellitus (number/%)	39 (14%)	1 (3%)	0.17
Diagnostic sleep efficiency (%)	78.9 (19.4)	73.3 (22.9)	0.17
Diagnostic REM (%)	9.3 (16.7)	7.4 (16.0)	0.69
Diagnostic AHI	35.8 (37.5)	40.9 (27.2)	0.47
Diagnostic CAI	0.0 (0.43)	0.9 (2.1)	< 0.001
Titration sleep efficiency (%)	94.9 (9.8)	90.3 (26.6)	0.04
Titration REM (%)	24.0 (38.4)	34.9 (52.9)	0.42
Titration AHI	3.6 (5.9)	14.5 (15.6)	< 0.001
Titration CAI	0 (0.9)	7.3 (6.2)	< 0.001
Therapeutic CPAP level (cm H ₂ O)	9 (4)	10 (4)	0.26
Maximum CPAP level (cm H ₂ O)	10 (4)	10.5 (4.3)	0.27

Data are reported with as medians with interquartile ranges or number and percentage of total as appropriate.

Table 2—Average and maximum total and unintentional leak during titration in all subjects

	CAI < 5	CAI ≥ 5	p value
Average Leak (L/min)	45.5 (20.8)	51.0 (21.0)	0.06
Average Excess Leak (L/min)	19.0 (17.0)	24.5 (12.8)	0.06
Peak Leak (L/min)	59.5 (27.0)	75.0 (27.8)	0.003
Peak Excess Leak (L/min)	34.0 (20.8)	52.5 (24.0)	0.001

Data are presented as medians with interquartile ranges.

Table 3—Average and maximum total and unintentional leak during titration with nasal masks

	CAI < 5 N = 280	CAI ≥ 5 N = 30	p value
Average Leak (L/min)	42.0 (17.0)	50.0 (16.8)	0.001
Average Excess Leak (L/min)	18.0 (16.0)	25.5 (12.8)	0.005
Peak Leak (L/min)	57.0 (23.0)	74.5 (24.3)	< 0.001
Peak Excess Leak (L/min)	33.0 (21.0)	53.0 (22.8)	< 0.001

Data are presented as medians with interquartile ranges.

CAI < 5 group, peak leak and peak excess leak were 57.0 L/min and 33.0 L/min versus 74.5 L/min and 53.0 L/min in the CAI ≥ 5 group ($p < 0.001$ and $p < 0.001$, respectively).

DISCUSSION

During this study, we observed that both average and maximum leak were associated with the development of central apnea during CPAP titration, particularly in subjects using a nasal mask. These findings were independent of the applied CPAP level and comorbidities which were balanced between groups, which may have confounded prior reports of complex apnea. We believe that nasal masks may be particularly problematic in predisposing to central apneas since the fresh gas can easily wash out the anatomical dead space when exiting through the mouth. However, oro-nasal masks may worsen pharyngeal mechanics by forcing the mandible posteriorly. Thus, treatment decisions may need to be individualized at least for certain patients.

The development of central apnea while on CPAP has a number of important physiological implications. The

evolutionary advantage of anatomical dead space has often been questioned, since the “wasting” of 25% to 30% of each breath would seem inefficient upon initial consideration. Some have suggested that the development of speech may have required anatomical dead space rather than a respiratory apparatus with no ability to control airflow. However, one interpretation of our findings, albeit speculative, might be that the anatomical dead space provides stabilization of breathing. That is, without anatomical dead space, the propensity for breathing instability would be high in response to perturbations (for example, ascent to altitude, exercise, cardiac disease). Assuming typical minute ventilation and CO₂ production, one would calculate that a 28 mL change in dead space would yield a 3 mm Hg fall in PaCO₂. Depending on the prevailing CO₂ apnea threshold, even a small change in dead space may produce central apnea in susceptible individuals.²³ Although one might predict a lowering of minute ventilation to occur in the face of hypocapnia, such a response is clearly not observed to an adequate extent among those patients who develop central apnea. Thus, mechanoreceptive and chemoreceptive homeostatic

mechanisms are clearly inadequate to eliminate central apnea acutely. However, based on our study design we have no way of proving that leak caused central apneas or instead was a marker of overtitration (or other factors) that yielded central apnea by other mechanisms (for example, pulmonary stretch or upper airway dilation). The fact that not all CPAP-treated patients develop central apnea may speak to the importance of raising end-expiratory lung volume such that larger lung volumes, and therefore greater gas stores, may improve breathing stability on CPAP. Moreover, the fact that oral appliance-induced central apnea is extremely rarely reported²⁴ suggests that mechanisms beyond upper airway opening are important in yielding central apnea.

Classic literature by Fowler et al. has reported marked reductions in dead space through expiratory breathhold.²⁵ The authors surmised that mixing would occur in the distal airways, such that a pause in breathing would facilitate CO₂ excretion as they observed with experimental measurements. The authors described a moving of the peripheral boundary of pure inspired gas up the bronchial tree during breathhold. In theory, a central apnea may produce similar physiology such that CO₂ may be cleared from the distal airways via diffusion and potentially cardioballistic mixing. Thus, the development of central apnea may further increase the propensity for PaCO₂ lowering by mechanisms described by Fowler in the 1940s. The combination of CO₂ elimination from the proximal airways by CPAP (via leak) plus the Fowler mechanisms during breathhold may work together to perpetuate central apnea. The fact that treatment-emergent central apnea generally resolves over time suggests that either resolution of leak or alteration of the chemical apnea threshold is occurring over time.

Despite its strengths, our study has a number of limitations which we acknowledge. First, we did not measure PetCO₂ or minute ventilation using gold standard pneumotachometers via a sealed nasal mask. Our goal was to perform a clinical study whereby patients were receiving usual care rather than being heavily instrumented, as normally is performed in our physiology laboratory. Some authors have suggested that treatment-emergent central apneas may be a function of poor sleep quality (i.e., state transition apneas),¹³ and thus our goal was to give standard instrumentation for clinical polysomnography rather than for an invasive physiological study. Moreover, a tightly sealed nasal mask to assess airflow would have defeated the purpose of our study from the standpoint of leak assessment. Second, we did not quantify changes in chest wall movement (lung volume), which may have been helpful to test the hypothesis that pulmonary stretch was having an important effect on ventilatory motor output. However, again, our goal was to perform a clinical real-world study rather than a physiological investigation. Chest wall movement is difficult to quantify in obese patients, and some increase in chest wall excursion would be expected while on CPAP. Thus, magnetometer or calibrated impedance bands would have been of interest but would not have yielded definitive data. Third, we did not systematically track adherence to CPAP among our participants in the long term. We have data on patients who received their PAP equipment from our sleep laboratory (although others receive equipment through a variety of home care companies) but did not receive ethics approval to track

the patients who left our sleep laboratory for PAP treatment. Among those patients who received CPAP from our sleep laboratory, adherence was, if anything, slightly better among those patients who developed central apneas (5.1 h/night) as compared to those who did not develop central apneas (4.1 h/night). However, we would emphasize that these data represent only 212 of the total of 310 participants and may not be representative since the source of equipment may be affected by insurance coverage, socioeconomic status, etc. Thus, we cannot draw any definitive conclusions about how complex apnea may influence long-term CPAP adherence from our data. Despite these limitations, we believe that our results are interesting and that our findings are robust given the constraints of a clinical study.

In conclusion, air leak has an important association with the development of treatment-emergent central apnea, independent of applied CPAP level and common comorbidities associated with central apnea. The underlying mechanism is not clear, but we speculate that proximal airway CO₂ elimination in the setting of leak as well as breathhold mechanisms described by Fowler et al. are important contributors. It is likely that with time either the leak resolves and/or the apnea threshold is reset resulting in cessation of central apneas. Whether efforts to eliminate mask leak will lead to abrupt resolution of central apneas will require further study. While further investigation is needed, our results add to the growing body of information on treatment-emergent central apneas and may speak to some evolutionary advantage for anatomical dead space which has been previously regarded as “wasted ventilation.”

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