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SCIENTIFIC INVESTIGATIONS

Expiratory Time Constant and Sleep Apnea Severity in the Overlap Syndrome

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Study Objectives: Lung mechanics in the overlap of COPD and sleep apnea impact the severity of sleep apnea. Specifically, increased lung compliance with hyperinflation protects against sleep apnea, whereas increased airway resistance worsens sleep apnea. We sought to assess whether the expiratory time constant, which reflects lung mechanics, is associated with sleep apnea severity in such patients.

Methods: Polysomnographies in 34 subjects with the overlap syndrome were reviewed. Three time constants were measured for each of up to 5 stages (wake, NREM stages, and REM). The time constants were derived by fitting time and pressure coordinates on the expiratory portion of a nasal pressure signal along an exponentially decaying equation, and solving for the time constant. Demographics, morphometrics, wake end-tidal CO_2, right diaphragmatic arc on a chest radiograph, and the apnea-hypopnea index (AHI) were recorded.

Results: The time constant was not associated with age, gender, body mass index, right diaphragmatic arc, or wake end-tidal CO_2, and was not significantly different between sleep stages. A mean time constant (TC) was therefore obtained. Subjects with a TC > 0.5 seconds had a greater AHI than those with a TC ≤ 0.5 seconds (median AHI 58 vs. 18, respectively, p = 0.003; Odds ratio of severe sleep apnea 10.6, 95% CI 3.9–51.1, p = 0.005).

Conclusions: A larger time constant in the overlap syndrome is associated with increased odds of severe sleep apnea, suggesting a greater importance of airway resistance relative to lung compliance in sleep apnea causation in these subjects.

Keywords: obstructive sleep apnea severity, chronic obstructive pulmonary disease, expiratory airflow, respiratory mechanics

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INTRODUCTION

During breathing, the pattern of expiratory flow reflects the mechanical properties of the lung. For instance, under conditions of passive expiration, the decay follows an exponential course from which a time constant can be derived. This time constant reflects the time required for the expiratory flow to decay to 37% of its peak value at the beginning of expiration. As such, the time constant is a measure of the tempo of emptying of the lungs during exhalation, and a function of the lung mechanics. Under ideal circumstances of passive expiration and single compartment model, the time constant is the product of airway resistance and lung compliance.[1,2]

Both lung compliance and airway resistance are increased in chronic obstructive pulmonary disease (COPD), delaying lung emptying and prolonging the expiratory time constant. The overlap syndrome, representing a combination of COPD and obstructive sleep apnea syndrome (OSAS), therefore provides a unique opportunity to evaluate the potential impact of impaired lung mechanics, as reflected by the time constant, on the severity of the apnea-hypopnea index (AHI). For instance, increased compliance and hyperinflation from COPD may reduce the severity of OSAS by increasing the traction on the upper airway and reducing its collapsibility.[3,4] In contrast, an increase in lower airway resistance may increase the negative inspiratory pressure and promote obstructive sleep apnea.[5]

BRIEF SUMMARY

Current Knowledge/Study Rationale: The expiratory time constant on the expiratory portion of a nasal pressure signal obtained during polysomnography reflects lung mechanics. We sought to assess whether that time constant is associated with sleep apnea severity in subjects who have both impaired lung mechanics from COPD and sleep disordered breathing from sleep apnea.

Study Impact: Our findings indicate that increased airway resistance may contribute to the development of obstructive sleep apnea in the overlap syndrome, suggesting a potential role for interventions that reduce airway resistance in the management of obstructive sleep apnea in this context.

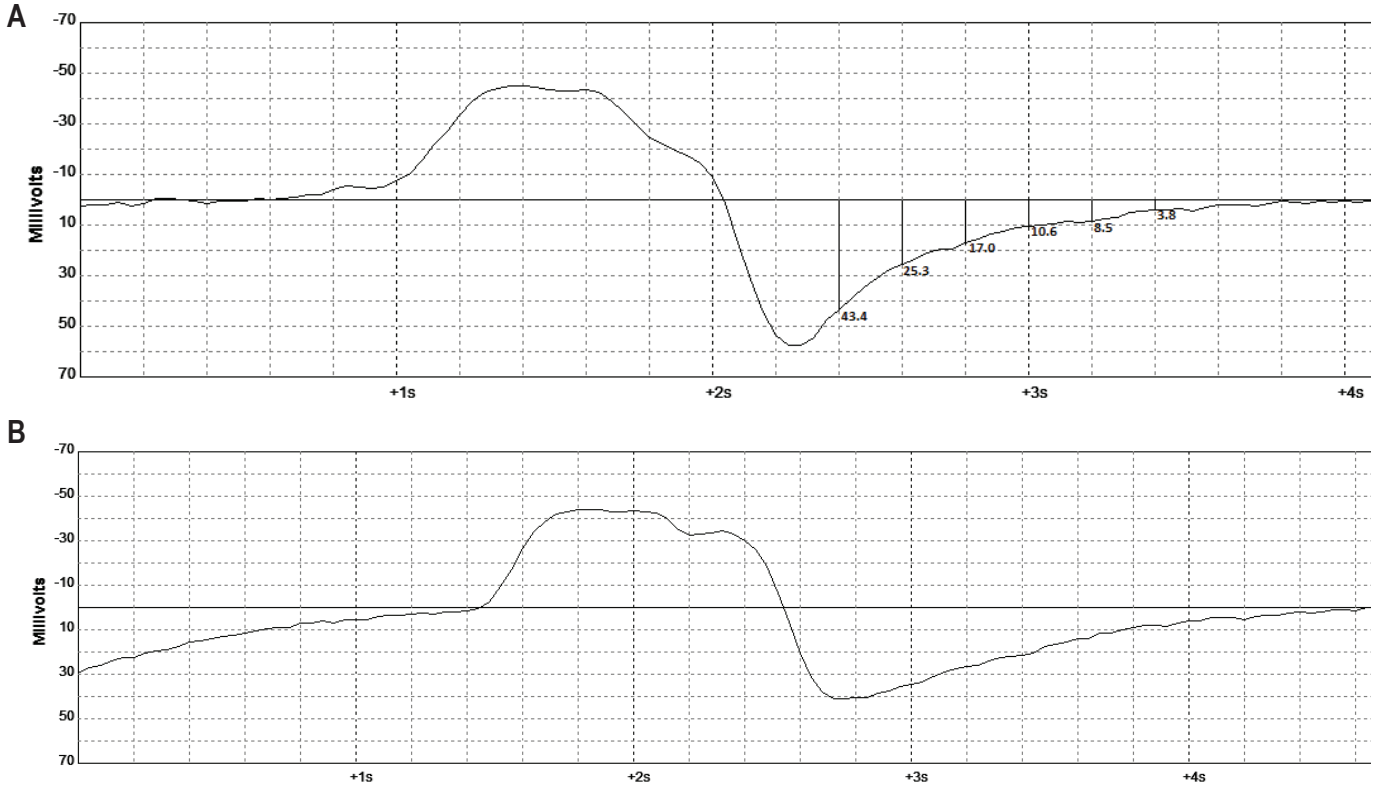
We therefore sought to study patients with the overlap of COPD and OSAS to assess primarily the potential association and directionality of the association between the expiratory time constant (as obtained from the nasal pressure signal during polysomnography) and the AHI, and secondarily whether the time constant differs across sleep stages from variations of lung volumes and airway resistance.[6]

METHODS

Subject Selection

This study used a cohort of adult subjects with both COPD and OSAS (overlap syndrome) from a previous study.[7] From this

Figure 1—Inspiratory and expiratory portion of two breaths.



Zoomed-in view of the inspiratory and expiratory portion of two breaths captured on a nasal pressure signal during polysomnography that are representative of those we selected for analysis. Inspiration has negative amplitude readings that follow a sinusoidal pattern above the zero baseline in the absence of flow limitation, whereas expiration has positive amplitude readings that follow an exponential pattern of decay from peak expiration back to the zero baseline in the context of passive expiration (appearing as a downward concavity). Time markers at 0.2 second intervals are shown in panel A. Six coordinates are measured from the first time marker after the peak expiratory flow to the last marker before return to the zero baseline. The amplitude is the deflection from baseline in millivolts, as determined by placing the cursor on the display at the corresponding time coordinate. **(A)** Patient with FEV_1 48% predicted and apnea-hypopnea index of 17.4. The expiratory time constant in this tracing is 0.44 (see derivation in Figure 2). **(B)** Patient with FEV_1 71% predicted and apnea-hypopnea index of 61. The expiratory time constant in this tracing is 0.59. The longer time constant in panel B relative to panel A can be visually appreciated by the flatter concavity and a slower return to the baseline.

cohort, we selected those with a complete full-night polysomnography. The diagnosis of COPD was confirmed by review of the medical records for a clinical diagnosis of COPD along with spirometry showing a post-bronchodilator forced expiratory volume in 1 second to forced vital capacity ratio (FEV_1/FVC) of < 0.70.[8] OSAS was defined as an AHI ≥ 5 along with signs or symptoms of disturbed sleep.[9]

Measurements

The oral/nasal cannula used for pressure monitoring (Salter 5744 from Salter labs, Lake Forest, IL) was positioned with the tip of the prongs inside the nose, and connected to a pressure transducer with a sampling rate of 25 Hz. Predicted variables for the spirometry used the Third National Health and Nutrition Examination Survey reference.[10] Predicted values for lung volumes and diffusing capacity used Crapo and Miller references, respectively.[11,12] All sleep studies were full-night attended laboratory polysomnographies, manually scored by technicians and then reviewed by board-certified sleep medicine physicians using the 2007 scoring rules of the American Academy of Sleep Medicine.[13]

The expiratory portion of selected breaths, as captured on a nasal pressure transduced signal was analyzed. We excluded breaths that were part of a sleep disordered breathing sequence (including those with apnea on the thermistor channel, hypopnea or flow limitation on the nasal pressure signal), breaths with significant artifacts, and those with a convex appearance to the expiratory flow, perhaps indicating extension of inspiratory muscle activity into expiration.[2] **Figures 1A** and **1B** are representative of selected breaths. A time constant was derived by selecting 6 time and nasal pressure coordinates at 0.2-s intervals along the expiratory portion of a nasal pressure signal, between the peak expiratory flow and the return to zero flow (**Figure 1**), fitting those 6 coordinates along an exponentially decaying equation $P(t) = P(0)*e^{(-t/\tau)}$, and solving for the expiratory time constant τ (**Figure 2**).[14] To ensure adequate passive expiration and signal quality, waveforms with a coefficient of determination (R^2) ≥ 0.95 were selected, indicating that ≥ 95% of the variance in the nasal pressure signal is explained by the regression equation and that the equation reliably matches the actual data with little loss of information, thereby ensuring that the derived time constants are accurate.

Three time constants were measured for each stage from wake through stage N1, N2, N3, and REM sleep for up to 15 estimates per patient. We obtained demographic data (age, gender), morphometrics (body mass index), Epworth Sleepiness Scale, spirometry data (FEV_1% predicted), polysomnographic data (AHI, REM sleep stage as percent total sleep time, the percent of sleep spent at an oxygen saturation level < 90%, the percent of sleep spent in the supine position, awake end-tidal carbon dioxide [CO_2]), as well as lung volumes and diffusion capacity when available. The right diaphragmatic arc, a measure of hyperinflation which has been found to correlate significantly with pulmonary function tests, was also recorded.[15]

Statistical Analysis

Linear mixed model was performed to assess the association between time constant and variables of interest, with sleep stages as a fixed effect, and accounting for the correlation within subjects. Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range), with comparison of variables between groups performed by *t* tests or the Mann-Whitney *U* test depending on the data distribution (normal or non-normal respectively). Two-by-two cross-tabulation analyses were performed using the χ^2 test or, alternatively, the Fisher exact test when any cell of the contingency table contained < 5 counts. Significance was defined as $p < 0.05$. SAS version 9.3 (SAS Institute Cary, NC) was used in the linear mixed model and SPSS 11.5 (SPSS, Chicago IL) for other analyses. This study was approved by the investigational review board of the Cleveland Clinic.

RESULTS

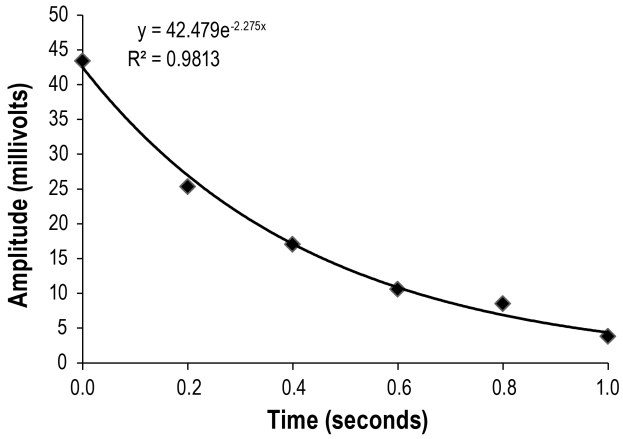
Of the 48 subjects of the original cohort of patients with the overlap syndrome,[7] 34 had complete full-night diagnostic polysomnography available for review. A mixed model analysis showed no significant differences in the time constant between sleep or wake stages, and there was no significant association between various variables and the time constant, except for a significant positive correlation with the percent of supine sleep (**Table 1**).

As there was no difference in time constant τ between sleep or wake stages, we obtained an average time constant (TC) from those obtained across all stages. The mean TC was 0.60 s with a non-normal distribution, and median TC (interquartile range) 0.48 (0.30–0.67) seconds.

Comparing groups separated by a rounded up median TC of 0.5 s (with 17 subjects in each group), the median AHI (interquartile range) was 17.5 (11.6–29.4) for overlap subjects with time constant ≤ 0.5 sec and 57.6 (31.1–74.9) for those with a time constant > 0.5 sec ($p = 0.003$) (**Table 2** and **Figure 3**).

Using the same cutoff, a longer TC was also predictive of severe sleep apnea: 23.5% (4 of 17) of overlap subjects with a TC ≤ 0.5 s had severe sleep apnea, compared to 76.5% (13 of 17) of those with a time constant > 0.5 s ($p = 0.005$) (**Table 2**). The odds ratio that a long TC is associated with severe sleep apnea was 10.6 (95% confidence interval [CI]: 3.9–51.1). A sensitivity analysis with receiver operating characteristic curve confirmed that a TC of 0.50 was an appropriate cutoff, with 77% sensitivity, 67% specificity, and 77% and 67% positive and negative predictive value, respectively, for severe sleep apnea. Otherwise, the gender distribution, FEV_1 % predicted, age, body mass index, Epworth Sleepiness Scale, right diaphragmatic arc, supine sleep, rapid eye movement (REM) sleep, and saturation < 90% (all as percent of total sleep time), lung volumes, diffusion capacity, and wake end-tidal CO_2 were not significantly different between subjects with and without a short time constant (**Table 2**).

Figure 2



Coordinates obtained from Figure 1A are plotted with the first coordinate arbitrarily set at time 0. A trend line with exponential fit is shown, along with the corresponding equation and R^2. In this example the time constant $\tau = 1/2.275 = 0.44$ seconds and the R^2 is 0.98.

Table 1—Linear mixed model for association between various variables and the time constant (in milliseconds).

Variables	Coefficients (95% CI)[a]	p value
Apnea-hypopnea index (events/hour)	−1.7 (−8.4, 5.1)	0.63
Supine sleep (% of TST)	6.6 (0.90, 12.3)	0.03
Saturation < 90% (% of TST)	−3.5 (−9.3, 2.3)	0.25
Gender (Male − Female)	198 (−199, 594)	0.34
Age (years)	−2.2 (−24.0, 19.7)	0.85
Body mass index (kg/m^2)	−20.5 (−54.5, 13.5)	0.25
Epworth Sleepiness Scale	−11.1 (−45.6, 23.4)	0.53
Wake end-tidal CO_2 (mm Hg)	2.0 (−27.6, 31.6)	0.89
FEV_1 (% predicted)	−1.8 (−13.5, 9.8)	0.76
Right diaphragmatic arc (cm)	51.5 (−111, 214)	0.54

[a]Coefficients refer to the change in time constant in milliseconds when the variable increased one unit. For gender, the coefficient refers to the change in time constant in male relative to female gender. TST, total sleep time.

DISCUSSION

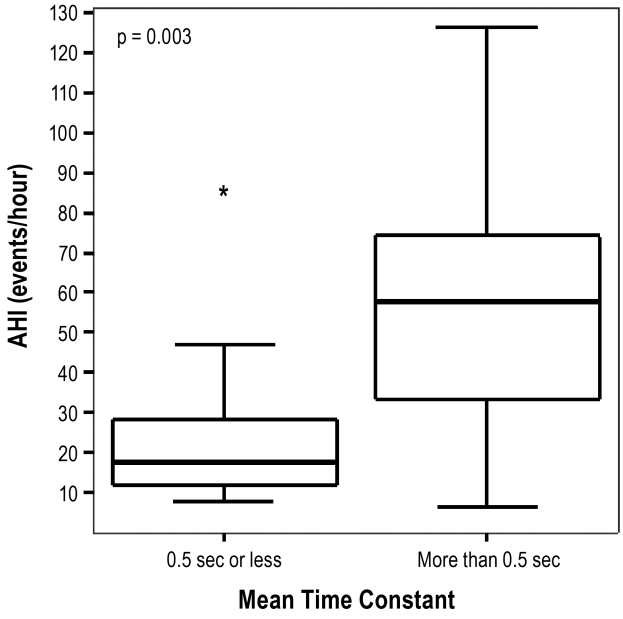
This study demonstrates that in the overlap syndrome (COPD and OSAS), an expiratory time constant greater than > 0.5 s (obtained from an average of up to 15 nasal pressure readings with

Table 2—Demographic, morphometrics, and polysomnographic data, overall and by mean time constant cutoff.

Variables	Overall[a]	Mean Time Constant ≤ 0.5 sec[a]	Mean Time Constant > 0.5 sec[a]	p value
Apnea-hypopnea index (/h)	29.7 (14.5–69.1)	17.5 (11.6–29.4)	57.6 (31.1–74.9)	0.003[b]
Percent with AHI ≥ 30	50	23.5	76.5	0.005[c]
Supine sleep (% of TST)	39.5 (14.2–74.5)	27.5 (9.2–56.3)	45.7 (25.5–97.9)	0.09[b]
REM sleep (% of TST)	13.6 (7.8–18.2)	12.8 (7.4–19.5)	13.6 (8.3–18.3)	0.67[b]
Saturation < 90% (% of TST)	39.4 (6.4–72.4)	37.9 (1.8–81.8)	40.8 (7.8–64.2)	0.81[b]
Percent male/female	53/47	47/53	59/41	0.73[d]
Age (years)	67.4 ± 9.3	67.3 ± 8.0	67.5 ± 10.7	0.94[e]
Body mass index (kg/m^2)	32.8 (29.1–36.5)	32.1 (29.8–37.3)	33.8 (29.5–36.5)	0.54[b]
Epworth sleepiness scale	10.7 ± 5.9	11.9 ± 6.0	9.4 ± 5.6	0.22[e]
Wake end-tidal CO_2 (mm Hg)	36.0 ± 7.3	35.0 ± 9.7	37.0 ± 3.8	0.45[e]
FEV_1 (% predicted)	59.7 ± 17.4	56.9 ± 14.1	62.58 ± 20.2	0.35[e]
Right diaphragm arc (cm)	2.5 (1.9–3.5)	2.6 (1.9–3.7)	2.8 (1.9–3.4)	0.78[b]
Total lung capacity (% predicted)	106.6 ± 12.1 (n = 14)	105.7 ± 7.6 (n = 7)	107.6 ± 16.0 (n = 7)	0.79[e]
Residual volume (% predicted)	147 ± 33.9 (n = 14)	145.7 ± 33.9 (n = 7)	148 ± 36.4 (n = 7)	0.89[e]
Diffusing capacity (% predicted)	60.3 ± 17.9 (n = 24)	58.6 ± 18.8 (n = 13)	62.1 ± 17.5 (n = 11)	0.64[e]

Data shown as mean ± standard deviation, median (interquartile range), or percent. [a]34 patients overall (17 in each group) unless otherwise specified, [b]Mann-Whitney U test, [c]Fisher exact t-test, [d]χ^2 test, [e]t-test. FEV_1, forced expiratory volume in the first second; TST, total sleep time.

Figure 3—Box plot of AHI distributions in individuals with short vs. long time constant.



The box represents the interquartile range. The line within the box represents the median. Vertical lines represent the range excluding outliers (shown with an *).

equal representations of wake, NREM stages, and REM stages), is associated with a nearly 11-fold increase in odds of severe sleep apnea. Potential important confounders of the sleep apnea and COPD severity, such as age, gender, morphometrics, Epworth Sleepiness Scale, FEV_1 percent, hyperinflation as measured by the right diaphragmatic arc or lung volumes, and the wake end-tidal CO_2, were not significantly different between groups with a short or those with a long time constant. We were not able to demonstrate a difference in time constant between sleep stages.

Our estimation of the time constant was based on a measurement of the amplitude of the pressure signal at several time points in the expiratory phase of patients with the overlap syndrome, and fitting the coordinates into an exponential decay model to solve for the time constant.[16] The assumptions with that approach are that expiration is passive,[2] and that the behavior of the respiratory system follows a single compartment model.[16] The condition of passive expiration is more likely to occur in patients with COPD relative to normal individuals where inspiratory muscle activity may continue into expiration,[2] and perhaps also more likely to occur during sleep. For instance, studies have shown that unlike normal individuals, subjects with severe airway obstruction have no or reduced extension of inspiratory muscle activity into expiration, with absent electromyographic signal, indicating relaxed expiratory muscles through expiration.[17,18]

A significant limitation of our technique is that a nasal pressure signal was used as a correlate of flow.[19,20] The nasal cannula pressure-transduced signal obtained during polysomnography closely mirrors airflow. Specifically, this signal has an excellent dynamic response to the airflow profile, a linear quantitative correspondence to flow within the normal rage of breathing, and can detect flow limitation.[20] However, the relationship between nasal pressure and flow is best described as quadratic (Rorher model) rather than linear.[16,19,20] Realizing that turbulent flow contributes more to the pressure, a square root correction for the nasal pressure signal was proposed as a better linear correlate of flow, though predominantly in inspiration rather than expiration.[21]

A further limitation of our method is that heterogeneity of lung emptying in the presence of lung disease challenges our concept of a single compartment model of the lung.[14,22,23] This model consists of a single flow unit with a constant resistance, in series with a single elastic unit of constant compliance.[16] However, there are significant differences in the time constant

when it is measured at different lung volumes in subjects with lung disease.[22–24] Specifically, in patients with the acute respiratory distress syndrome and those with COPD, the time constant increases as expiration proceeds.[22,23] Notably, a single compartment cannot accurately describe passive expiration in intubated and paralyzed patients.[25] However, our patients were in a stable state in the outpatient setting, as opposed to intubated under conditions of respiratory failure,[14,23] or paralysis.[24]

The time constant derived from flow decay ideally equals the product of resistance and compliance, similar to the behavior of an electrical RC circuit (resistance and capacitance in series).[2,14,16] While the expiratory pressure decay over time had an excellent exponential fit ($R^2 \geq 0.95$) in our data, our assumptions of proportionality of nasal pressure to flow, and of a single compartment model, suggest that our model can best provide an effective time constant rather than one that accurately reflects the product of resistance and compliance.[14]

This effective time constant nevertheless reflects lung mechanics given its association with severe sleep apnea. For example, using published estimates for the coefficients of the Rorher model quadratic relationship between pressure and flow during expiration, our technique can be assessed to reflect the product of resistance and compliance but underestimates it by a factor of 1.8.[21]

Other investigators derived the time constant from various variations of the ratio or slope of volume to flow through a modification of the equation of motion,[26] and found similar relationships between the time constant and intrinsic mechanical properties of the lung. For example, two groups found a logarithmic correlation between the FEV_1 and the time constant in patients with obstructive lung disease, and the time constant can differentiate between subjects with and those without COPD. [2,14] Moreover, the time constant can be used to accurately calculate the time needed for complete expiration (estimated as being 3 times the time constant and used as an indicator of the severity of COPD) as demonstrated in mechanically ventilated subjects with COPD.[23]

Our technique lacks enough sensitivity to detect changes in the time constant with severity of FEV_1 as was shown in other studies.[2,14] Our results may be also influenced by the small number of patients in our study, the sampling of only 3 readings per sleep stage per patient, selection of patients in the outpatient setting and therefore more stable COPD, determination of tracings predominantly during sleep, and the context of a nasal pressure signal with potential for significant air leakage. Automated software algorithms within the polysomnography programs may increase the number of time constant samplings across wake and sleep stages and detect subtle variations in lung mechanics across those stages, and with disease severity.

The relative contribution of the upper versus lower airway resistance to the time constant cannot be determined from our data. For instance, the association we found between supine sleep and the time constant may reflect narrowing of the upper airway in the supine position. However, in studies performed during wake that similarly did not separate the upper from lower airway components of the airway resistance, there was either no difference in lung mechanics (compliance or resistance) between supine and lateral positions,[27] or a decrease in the time constant in the supine relative to the lateral position.[28] Moreover, in our study, a model incorporating both short vs. long time constant, and percent supine sleep as predictors of severe sleep apnea, only a long time constant remained a significant predictor of severe sleep apnea. This suggests that the supine position did not confound the association between a long time constant and severe sleep apnea. The relationship between the supine position and the time constant therefore may reflect the additional effect of the supine position on lung volumes and pulmonary (rather than upper airways) mechanics.

While our determination of the expiratory time constant for unobstructed breaths may have reduced the impact of upper airway resistance on the time constant, studies have shown that the upper airways (retropalatal and retroglossal) are narrower in expiration in OSAS than normal, narrowest at the end of expiration, though larger relative to inspiration at equivalent tidal volumes.[29,30] During sleep, the expected loss of upper pharyngeal muscle tone contributes to an increase in upper airway resistance,[31–33] especially in COPD where increased nocturnal CO_2 reduces the supraglottic resistance less than in normal subjects.[34] However, we were unable to document a correlation between the time constant and the AHI, nor changes in the time constant across sleep stages or relative to wake, either due to the low sensitivity of our technique or because of a greater contribution of the lower rather than upper airway resistance, especially in the context of COPD.

Our study has interesting potential clinical applications. Specifically, it adds impaired lung mechanics, perhaps more specifically pulmonary or lower airway resistance, as a risk factor to the development of obstructive sleep apnea, in addition to conventional predictors of sleep apnea such as obesity or male gender. While the prevalence of OSAS in COPD is not higher than that of subjects without COPD,[35] and while the long acting bronchodilator salmeterol did not change the AHI in OSAS without obstructive airway disease,[5] our study suggests that future studies may target an overlap syndrome population with severe sleep apnea, to assess whether therapeutic measures that reduce lower airway resistance also improve reduces the AHI. Already, bronchodilators have been suggested to reduce apnea severity in the overlap syndrome by reducing the maximal inspiratory negative pressure,[5] asthma was identified as an independent risk factors for the development of snoring,[36] and inhaled fluticasone propionate was found to improve the pharyngeal critical pressure (Pcrit) in controlled asthma.[37] The alternative hypothesis of a longer time constant due to higher compliance with hyperinflation would have been expected to protect against the development of sleep apnea,[3,4] and we did not find a difference in lung volumes in patients with and without a long time constant.

In conclusion, we demonstrate that a novel technique that assesses the time constant from the decay of the expiratory pressure signal during polysomnography in the overlap syndrome reflects lung mechanics with sufficient sensitivity and specificity to identify a risk for severe sleep apnea. This finding suggests a role for increased airway resistance in the development of obstructive sleep apnea and a potential role for interventions that reduce airway resistance in the management of obstructive sleep apnea.

ABBREVIATIONS

AHI, apnea-hypopnea index
CI, confidence interval
CO_2, carbon dioxide
COPD , chronic obstructive pulmonary disease
FEV_1, forced expiratory volume in 1 second
FVC, forced vital capacity
NREM, non-rapid eye movement
OSAS, obstructive sleep apnea syndrome
REM, rapid eye movement
SD, standard deviation
TC, time constant

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