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Variability of respiratory mechanics during sleep in overweight and obese subjects with and without asthma

L.M. Campana^{1,2}, R.L. Owens², J.P. Butler², B.S. Suki¹, and A. Malhotra²

¹Department of Biomedical Engineering, Boston University, Boston, MA 02215

²Division of Sleep Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School. Boston, MA 02115

Abstract

Variability of respiration may provide information regarding disease states. We sought to characterize variability of ventilation and resistance in healthy and asthma, to determine how respiratory control may be altered in sleep and with bi-level positive airway pressure (BPAP). Overweight and obese subjects with and without asthma were studied during sleep at baseline and with BPAP, while measuring respiratory system resistance (R_{rs}) continuously. Stable periods (>20min) of wake, NREM, and REM sleep were identified and correlation metrics of respiratory parameters were calculated, including coefficient of variation (CV). Variability of R_{rs} was also characterized over short time scales (20 breaths) during sleep and defined as either “leading to arousal” or “not leading to arousal”. Data from 10 control and 10 subjects with asthma were analyzed. CV of R_{rs} was decreased in asthma at baseline ($p<0.001$) and decreased on BPAP as compared to baseline ($p<0.001$). Long time scale correlations were found in respiratory parameters, but the degree of correlations was decreased from wake to sleep ($p<0.05$). The variance and CV of R_{rs} was increased preceding an arousal from sleep at baseline; however, during BPAP, the CV was decreased and was not increased preceding arousals. At baseline, resistance was greater in those with asthma, but variability was smaller. BPAP reduced both resistance and overall variability. We conclude that the BPAP-induced decrease in variability may indicate that those with asthma are more likely to remain in a low resistance state, and that low resistance variability may reduce arousals from sleep.

Keywords

Variability; resistance; arousals; ventilation; asthma

1. Introduction

Variability in biological signals such as heart rate has created considerable interest, particularly due to the potential prognostic value of heart rate variability in predicting

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Correspondence: Lisa Campana, 221 Longwood Ave 036 BLI, Boston, MA 02115, 617-732-8450, lcampana@bu.edu.

Disclosures

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mortality following myocardial infarction (Bauer et al., 2009; Bigger et al., 1993; Kleiger et al., 1987). By extension, some authors have assessed respiratory variability, particularly in patients with lung disease (Bien et al., 2011; Brack et al., 2002; Giraldo et al., 2004; Que et al., 2001). However, despite the major interest in breathing disorders during sleep, minimal work has been performed regarding breathing variability.

Fluctuations of respiratory variables are likely due to a combination of factors including nonlinear homeostatic and feedback processes, behavioral influences, and external stimuli (Suki, 2002). The variability of respiratory drive and respiratory impedance has been characterized during wakefulness (Brack et al., 1998, 2002; Muskulus et al., 2010; Que et al., 2001), but less is known regarding breathing variability during sleep. During sleep, behavioral influences are minimal; hence, the fluctuations are primarily driven by underlying feedback control mechanisms. Furthermore, analyzing respiratory variables during sleep allows one to collect large segments of data and to examine fluctuations over both short and long time scales.

Of clinical interest are respiratory diseases that worsen with sleep, such as asthma. Nocturnal worsening of asthma has been described for centuries and conveys a poor prognosis, although the underlying mechanism is unknown. Based on the notion that deep inspirations may be bronchoprotective, we hypothesized that lack of breathing variability during sleep may be an important factor in promoting nocturnal bronchospasm. Increasing fluctuations of respiratory resistance, not just increased mean resistance, may be a marker for future asthma attack (Gulotta et al.). This hypothesis calls for characterizing fluctuations in respiratory variables in those with asthma, as compared with healthy controls during sleep.

The goal of this study was to characterize variability in respiratory resistance during sleep in those with asthma compared with healthy controls. Furthermore, we sought to understand how these variables were altered with application of bi-level positive airway pressure (BPAP) during sleep. BPAP increases functional residual capacity and tidal volumes during sleep and reduces total respiratory system resistance through the lowering of upper airway resistance (Campana et al., 2013). The change in lung volume and reduction in resistance may influence overall variability and alter respiratory control, which in turn may affect the long and short time scale correlations of resistance. Finally, we hypothesized that nocturnal arousals are preceded by increases in airway resistance and variability of resistance, particularly in those with asthma.

In order to test our hypotheses related to respiratory resistance variability during wake, stable sleep, and leading to arousals, we studied healthy controls and those with asthma during sleep over two study nights. We continuously measured airflow and resistance on a baseline night and on a night with BPAP.

2. Methods

2.1 Patient Selection and Screening

The protocol was approved by Brigham and Women's Hospital Institutional Review Board, and all subjects gave informed, written consent. Subjects with and without documented asthma were recruited. Subjects were participants in a prior study testing the effect of BPAP-induced lung stretch on airway mechanics during sleep (Campana et al., 2013); however, the results presented in the present manuscript are not previously reported. All subjects were overweight or obese (Body Mass Index ≥ 25 kg/m²), non-smokers (<10 pack-years) and non-habitual snorers.

2.2 Protocol

The full protocol details and subject selection are previously published and can be found in Campana et al. 2013 (Campana et al., 2013). Briefly, the study consisted of two overnight visits. Subjects arrived prior to their usual bedtime and were instrumented with standard polysomnographic equipment (electroencephalogram, electro-oculogram, electromyogram, respiratory belts) and a nasal mask (ComfortGel, Philips-Respironics Inc) attached to a pneumotachograph (Hans Rudolph). During one night subjects slept with BPAP applied via the nasal mask while on the other night they slept without positive pressure; the order of these nights was chosen randomly. An in house system was designed to deliver forced pressure oscillations at 8Hz (~1 cmH₂O peak to peak pressure swings) during the night, which was used to calculate resistance (Campana et al., 2012b). The full details of the system design and validation can be found in Campana et al. 2012 (Campana et al., 2012b).

2.3 Long Time Series Analysis

Non-overlapping 30 second intervals were scored using standard criteria (Iber C, 2007). The apnea hypopnea index (AHI) was calculated for each subject based on the data from the baseline night. The 8Hz oscillations were used to calculate respiratory system resistance. The system was validated with resistances of known value both with and without BPAP (Campana et al.).

Periods of 15 minutes of uninterrupted wakefulness, NREM sleep, and REM sleep were identified, with a minimum of 200 breaths in each time period in order to assess variability and correlation parameters. The flow was integrated to calculate volume and end inspiration and end expiration time points were identified using a peak detection program to find the local minimum and maximum points of the volume trace. Variables measured in each time period on a breath to breath basis included: tidal volume (V_t), minute ventilation ($\dot{V}_e$), inspiratory time (T_i), expiratory time (T_e), T_i+T_e (T_{tot}), and resistance at end inspiration ($R_{rs,i}$). Resistance values were excluded if they were negative or if the coherence (a measure of noise and non-linearities) was <0.90 (Campana et al., 2013). If T_i for a given breath was greater than 3 sec or T_{tot} was greater than 10 sec, it was assumed that the peak detection algorithm missed a breath and the V_t , $\dot{V}_e$, T_i , and T_e were set to their interpolated averages of preceding and subsequent breaths. The total number of such events had to be less than 10% of the total length of the breath series for it to be included in the analysis.

Time series parameters—The mean (μ), standard deviation (σ), and coefficient of variation (CV) were calculated for each variable for each time period. The time series of length N breaths was then linearly detrended and the autocorrelation at lag 1 (AC) was calculated by

$$AC = \frac{\sum_{i=1}^{N-1} (X(i) - \bar{X}_1)(X(i+1) - \bar{X}_2)}{\sum_{i=1}^N (X(i) - \bar{X})^2} \quad (1)$$

where $\bar{X}$ is the mean value of the entire time series; $\bar{X}_1$ is the mean of the first $N-1$ points, and $\bar{X}_2$ is the mean of the last $N-1$ points.

Detrended fluctuation analysis—Detrended fluctuation analysis (DFA) was also performed on the data sets. For a time series $X(i)$ the mean was first subtracted and then the deviations around the mean were summed over breaths k (Equation 2).

$$Y(k) = \sum_{i=1}^k [X(i) - \bar{X}]. \quad (2)$$

$Y(k)$ was then divided into non-overlapping boxes of length n and a piecewise least-squares linear regression line was fit to each window of data. The root mean square of the fluctuations around the fit over all breaths N was calculated by Equation 3, and this process was repeated on multiple time scales n .

$$F(n) = \sqrt{\frac{1}{N} \sum_{k=1}^N [Y(k) - Y_n(k)]^2} \quad (3)$$

The relationship between the time scale n and the fluctuation $F(n)$ was found to follow a power-law relationship with a slope of α . In this case, when α is near 0.5 the fluctuations in the time series are occurring randomly with no long time scale correlations, if α is larger than 0.5 it is indicative of long range correlations in the time series. Since in many cases, $F(n)$ exhibited two separate regimes with different exponents, the resulting slope of the power law was found over short time scales (7–14 breaths, α_1) and longer time scales (15–50 breaths, α_2).

2.4 Arousals

Periods of NREM sleep were identified and the mean, variance (σ^2), CV, and AC of $R_{rs,I}$ were calculated over a moving window of 20 breaths on both the baseline and BPAP nights. If an arousal occurred during the next 10 breaths following the window, that window was defined as “leading to arousal” and if there was no arousal from sleep it was defined as “not leading to arousal”. Data from all subjects were pooled together, and the probability that the variance or CV was greater than any given value was calculated for those windows leading to arousal and not leading to arousal. This is equivalent to calculating 1- the empirical cumulative distribution function. From these curves we determined the likelihood of an arousal versus no arousal given the distributions of variance. The subjects with an AHI > 10 events/hr were excluded from the analysis, as an apnea or hypopnea could independently provoke an arousal from sleep (Iber C, 2007).

2.5 Statistical Analysis

To determine whether baseline differences existed over long time series between sleep stages (Wake vs. NREM vs. REM) or between healthy and asthma, a 2 way ANOVA was performed. A 3 way ANOVA was performed to determine if differences existed between sleep stages (NREM vs. REM), condition (healthy vs. asthma), or positive airway pressure (baseline vs. BPAP). For the arousal analysis, a Kolmogorov-Smirnov test was used to determine whether distributions were significantly different from one another.

3. Results

Ten healthy control and 10 asthma subjects were studied. Demographic information on the subjects and pulmonary function tests is shown in Table 1. At baseline, the average AHI in the control group was 14 ± 15 events/hr, with 3 subjects having an AHI > 10 events/hr. In the asthma group AHI was 4.4 ± 6.3 events/hr on average, with 1 subject having an AHI > 10 events/hr.

3.1 Long time series

Time series parameters—Mean resistance at end inspiration ($R_{rs,I}$) was higher in the asthma group as compared to the healthy controls ($p<0.01$), while the standard deviation of $R_{rs,I}$ was similar in the asthma and healthy groups. This finding is consistent with the observation that the CV of $R_{rs,I}$ was significantly lower in those with asthma as compared to healthy ($p<0.001$). No significant differences in $R_{rs,I}$ were found with changes in sleep stage. With BPAP application μ , σ , and CV of $R_{rs,I}$ were lower (μ : $p<0.01$, σ : $p<0.01$, CV: $p<0.001$) as compared to baseline, independent of disease state and sleep stage (Fig 1.). $R_{rs,I}$ was positively autocorrelated at a lag of 1 breath; however, this autocorrelation was not significantly different between healthy and asthma or between baseline and BPAP.

Detrended fluctuation analysis (DFA)—Shown in Table 2 and Table 3 are the grouped results of the DFA analysis. For all the time series the scaling exponent α was greater than 0.5 indicating long range correlations in respiratory parameters. The short time scale exponent, α_1 , was larger in REM sleep as compared to NREM and Wake in both V_t and $R_{rs,I}$ ($p<0.001$), but not in T_i . There was no significant change in α_1 with BPAP; however, there seemed to be a BPAP-sleep stage effect, with BPAP lowering the scaling exponent in REM sleep ($p<0.05$), but not in NREM. Over longer time scales (15–50 breaths) the scaling exponent, α_2 , was decreased in NREM sleep as compared to wake in V_t , T_i , and $R_{rs,I}$ ($p<0.05$). On the BPAP night, α_2 for V_t , T_i , and $R_{rs,I}$ was less during NREM sleep as compared to REM ($p<0.05$). There were no differences in α_1 or α_2 between asthma and healthy or between baseline and BPAP study nights.

3.2 Arousals

Data from the 7 healthy subjects and 9 asthma subjects with $AHI<10$ events/hr were pooled. In the healthy group at baseline, 827 windows of twenty breaths were analyzed; 10.9% of these windows were immediately followed by an arousal from sleep, while the remaining were not. When the healthy group was on BPAP, 846 windows were analyzed with 7.5% of them leading to arousal. In the asthma group at baseline, of 1040 windows 8.9% led to arousal. On the BPAP night 7.9% of 885 windows led to arousal. The cumulative distribution of the variance of $R_{rs,I}$ (Fig. 2) was significantly different between arousal and non arousal in both healthy ($p=0.02$) and asthma groups ($p<0.00001$) at baseline. Furthermore, CV of $R_{rs,I}$ (Fig. 3) at baseline was also significantly different between arousal and non-arousal (Healthy: $p=0.01$, Asthma: $p<0.00001$). On BPAP the variance and CV distributions are shifted to the left for both healthy and asthma. Furthermore, on BPAP the arousal and no arousal distributions are no longer significantly different in the asthma group ($p=0.63$). By determining the ratio of the arousal curve by the no arousal curve we obtain an odds ratio for a given variance (Fig. 2-Bottom) or CV (Fig. 3 -Bottom). These data imply that when the variance or CV of $R_{rs,I}$ is high in a window of 20 breaths, it is more likely to lead to an arousal from sleep, particularly in those with asthma. With BPAP application the odds ratio in the asthma group decreases, indicating that for any given value of the variance or CV the subject is equally as likely to have an arousal from sleep as to not.

4. Discussion

We have characterized the variability of resistance and tidal volumes during sleep in those with and without asthma. We have made several important observations. Our novel findings are: 1) those with asthma have reduced variability of resistance as compared to healthy controls at baseline during sleep. 2) Variability of resistance is reduced with BPAP application independent of disease. 3) Detrended fluctuation analysis results show positive long time scale correlations of resistance, tidal volumes and inspiratory times but differences exist between wakefulness, NREM, and REM sleep. 4) At baseline, variability of resistance

is increased preceding an arousal from sleep, particularly in those with asthma. 5) BPAP reduces the variability of resistance preceding arousals from sleep in those with asthma. To the authors' knowledge this is the first study to characterize fluctuations of resistance during sleep in an asthma population.

4.1 Long Time Series

At baseline, those with asthma have increased mean resistance and less variability compared to healthy subjects. With large mean values of resistance, and low variability, those with asthma will be more likely to stay in a high resistance regime which could theoretically lead to poorer asthma control. CV of resistance is unexpectedly lower in those with asthma as compared to controls at baseline. Que et al. (Que et al., 2001) reported increased variability of resistance in the asthma group as compared to healthy people; our results differ from theirs likely due to methodological differences. First, our study involved recordings of people during sleep, a state which would remove any behavioral influences on breathing variability. Second, the increased variability found in asthma was only seen when Z_{rs} was compared against the Z_{rs} of control subjects in a sitting position (Que et al., 2001). When control subjects were placed in a supine posture the standard deviation of impedance was increased, and the authors hypothesized that the drop in lung volume from sitting to supine caused the airway smooth muscle to unload leading to increased variability of resistance. All of our data were taken when subjects were in a supine posture and all of our subjects were overweight or obese which in turn may cause them to have low resting lung volumes, particularly when supine and during sleep. Finally, they calculated variability of respiratory system impedance over the entire breath cycle, while we assessed only end inspiratory values of R_{rs} . The end inspiration values may be more stable and less prone to variations than the entire breath cycle because the latter can be influenced by intra-breath upper airway opening and closing. We opted for defining one R_{rs} value per cycle as V_t and T_i parameters are only found on a breath to breath basis.

With BPAP application there was an increase in mean V_t (Campana et al., 2013) and a decrease in mean and standard deviation of resistance. Hence, CV of resistance was also decreased with BPAP. When on BPAP, those with asthma may be more likely to remain in a lower resistance state and perhaps will be less likely to reach the high levels of resistance (compared to controls) that increase the risk of nocturnal asthma symptoms.

Detrended fluctuation analysis—We found that while the power-law scaling exponent of resistance decreases from wake to sleep, it is larger than 0.5, indicating that the fluctuations in resistance during sleep are not independent from one another. This finding is true in both the healthy and asthma group and it suggests that during sleep there are fewer deterministic processes in respiratory control mechanisms influencing breathing. Fluctuations in resistance at 8Hz are likely a consequence of either changes in airway diameter, or changes in chest wall properties. Those with asthma have lower overall variability of respiratory parameters as measured by CV, but autocorrelations and DFA analysis are similar in control and asthmatics. Muskulus et al. (Muskulus et al., 2010) did not find any significant differences in the scaling exponent between asthma, COPD, and healthy controls during wakefulness; however, the scaling exponents of resistance were very close to 0.5, indicating no long term correlations. By contrast, our data show that during sleep, fluctuations in resistance are not completely random. Frey et al. found that increased variability in peak expiratory flow of those with asthma was associated with future asthma attacks, but the time scale of this variability was over weeks (Frey et al., 2005).

We also found distinct differences in breath size and timing with sleep stage consistent with what has been reported previously (Rostig et al., 2005; Schumann et al.) During NREM

sleep, the overall variability of V_t and T_i , as measured by CV, is decreased as compared to REM. Furthermore, α_1 and α_2 of V_t are larger with wake and REM sleep as compared to NREM sleep, similar to what is seen in resistance. This finding indicates that breathing is more stable during NREM sleep with less fluctuation than during REM sleep. Breathing during NREM sleep is being tightly controlled through metabolic feedback, while the influences of behavior and external stimuli are minimal. During NREM sleep respiratory patterns are driven by the mean output of the respiratory pattern generator and variability is more random, indicating decreased control of respiration. During REM sleep increased correlations are likely due to increased cortical influence on breathing activity. The degree of long time scale correlations in respiratory parameters is driven by increased brain activity occurring with wakefulness and REM sleep (Lu et al., 2006).

4.2 Arousals

Our analysis of arousals from sleep has led to several novel and interesting findings. When the variability of $R_{rs,I}$ increases, as measured by σ^2 or CV, it is more likely a subject will arouse from sleep. For example, in those with asthma, at baseline 60% of windows leading to arousal have a variance greater than 2 (cmH₂O/L/s)², while only 20% of windows not leading to an arousal have a variance greater than 2. Hence, given a variance of 2 (cmH₂O/L/s)² during 20 breaths, it is almost three times more likely that an arousal occurs within the next 10 breaths than not. The distance between the arousal and no arousal distributions as determined by the K-S test is larger in the asthma group compared to the healthy at baseline. Arousals in the asthma group are driven by changes in resistance variability, while in the healthy group arousals from sleep are more likely caused by other reasons not related to resistance fluctuations.

This concept is further supported by the effect of BPAP. We have found that BPAP can reduce mean and σ^2 of $R_{rs,I}$ (Fig. 1). With BPAP on, the distributions of σ^2 are markedly shifted to the left (Fig. 2) and there is no longer a difference between arousal and no arousal distributions in those with asthma. Revisiting our example above, a variance greater than 2 (cmH₂O/L/s)² occurs very infrequently when on BPAP, only 6% of the time in windows leading to arousal and 3% of the time in windows not leading to arousal. A portion of arousals that occur during baseline are driven by increased variability of $R_{rs,I}$, while on BPAP arousals are thus being driven by factors other than resistance variability. The total number of arousals per hour of sleep was not significantly different between baseline and BPAP, indicating that arousals due to other reasons (such as the BPAP itself) are increased.

The forced oscillation technique is a noninvasive way to monitor resistance fluctuations during sleep. Our data have shown that even when no clinical sleep apnea is present, resistance fluctuates greatly in those with asthma. Monitoring these fluctuations could provide a metric for determining asthma severity or the effectiveness of medication. By quantifying these parameters during sleep, behavioral influences which alter respiratory control are removed. BPAP has a strong effect on resistance variability. If a subset of people with asthma find BPAP minimally intrusive on their sleep quality it could be used to reduce resistance driven arousals from sleep, which in turn could have a beneficial impact on quality of life. Additionally, preventing such arousals may lead to a reduction in nocturnal asthma attacks. Our results could explain the finding that several studies in patients with asthma and OSA note subjective improvement in asthma symptoms with CPAP, although no objective improvements are seen in spirometry (Ciftci et al., 2005; Lafond et al., 2007).

4.3 Limitations

We acknowledge several limitations in our study. First, we had a small sample size due to the fact that these overnight studies are extremely labor and time intensive. Furthermore, we

had predominantly mild to moderate asthma patients. There was also a slight gender disparity between groups, with more women in our asthma group and more men in our control group. We attempted to recruit equal numbers of men and women but overall recruitment was limited due to the considerable time commitment and instrumentation involved with this study. We were also limited in the time scales used as we only had one night of data for baseline and one night for BPAP, given that correlations change with sleep stage, any interruptions in sleep limit the amount of continuous data. The variability of these parameters over longer time scales of days or weeks remains open. Further study is needed regarding respiratory variability in the asthma population.

4.4 Summary

Variation of respiration changes with sleep stage. NREM sleep is associated with stable breathing, with only small fluctuations occurring that are minimally correlated with one another. REM sleep exhibits strong long time scale correlations, presumably secondary to increased brain activity associated with phasic REM sleep. Resistance is larger in those with asthma, but overall variability as measured by CV is smaller; with BPAP application both the mean and variability decreases. The decrease in variability with BPAP may be important for a number of reasons: those with asthma may be more likely to remain in a low resistance state and low variability may reduce arousals from sleep. We believe that BPAP is a potential therapy for reducing fluctuations in airway resistance during sleep.

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Highlights

- Variability of respiratory parameters may provide information about disease states
- Mean resistance is increased while variability of resistance was decreased in those with asthma as compared to healthy
- Variability of resistance was increased preceding arousals from sleep
- Bi-level positive airway pressure reduced the variability of resistance preceding arousals from sleep

Figure 1.

A) Mean B) standard deviation C) CV and D) AC of respiratory system resistance at end inspiration for healthy and asthma on baseline and BPAP nights during wake (black), NREM (gray), and REM (light gray) sleep.

Figure 2.

Top: Probability that the variance is greater than a value for the asthma group for windows leading to arousal (dashed) and no arousal (solid) from sleep at baseline (black) and BPAP (gray). With BPAP, both the arousal and no arousal distributions shift left, to lower variances, and the difference between arousal and no arousal becomes insignificant. Middle: Data from the healthy group on baseline (black) and BPAP (gray) nights for arousal (dashed) and no arousal (solid) distributions. Bottom: The likelihood that given a value for the variance an arousal occurs relative to no arousal for Healthy (black) and Asthma (gray) at baseline (solid) and BPAP (dashed).

Figure 3.

Top: Probability that the CV is greater than a value for the asthma group for windows leading to arousal (dashed) and no arousal (solid) from sleep. Baseline data is shown in black and BPAP data is in gray. With BPAP, both the arousal and no arousal distributions shift left, to lower CVs, and the difference between arousal and no arousal becomes insignificant. Middle: Data from the healthy group on baseline (black) and BPAP (gray) nights for arousal (dashed) and no arousal (solid) distributions. Bottom: The likelihood that given a value for the CV an arousal occurs relative to no arousal for Healthy (black) and Asthma (gray) at baseline (solid) and BPAP (dashed)

Table 1

Subject Demographics

Group	N	Age (yrs)	Sex	BMI (kg/m ²)	PC20 (mg/ml)	FEV1 (L)	FEV1 (% pred)
Healthy	10	35 ± 15	6 M	31.9 ± 3.2	>25	4.0 ± 1.3	101 ± 12
Asthma	10	33 ± 14	2 M	33.6 ± 6.4	3.6 ± 5.2	2.7 ± 0.8	80 ± 19
P Value		0.67		0.47		0.01	0.01

Table 2 Short time scale scaling exponent α_1 for breaths 7–14

		Baseline		REM	BPAP	
		Wake	NREM		NREM	REM
Vt	Healthy	0.77 ± 0.2	0.69 ± 0.2	1.02 ± 0.3[*]	0.80 ± 0.1	0.88 ± 0.2
	Asthma	0.73 ± 0.2	0.63 ± 0.1	0.92 ± 0.2[*]	0.71 ± 0.2	0.88 ± 0.2
Ti	Healthy	0.85 ± 0.2	0.71 ± 0.1	0.73 ± 0.1	0.74 ± 0.1	0.65 ± 0.1
	Asthma	0.80 ± 0.1	0.68 ± 0.1	0.75 ± 0.1	0.68 ± 0.1	0.68 ± 0.1
Rrs I	Healthy	0.67 ± 0.1	0.71 ± 0.1	0.93 ± 0.2[*]	0.71 ± 0.1	0.72 ± 0.2
	Asthma	0.74 ± 0.1	0.68 ± 0.1	0.94 ± 0.1[*]	0.79 ± 0.1	0.77 ± 0.2

^{*} REM>NREM & REM>Wake, p<0.001

Table 3 Long time scale scaling exponent α_2 for breaths 15–50

		Baseline		BPAP	
		Wake	NREM	REM	REM
Vt	Healthy	0.76 ± 0.2	0.56 ± 0.2[*]	0.66 ± 0.2	0.55 ± 0.1[‡]
	Asthma	0.79 ± 0.2	0.63 ± 0.1[*]	0.78 ± 0.1	0.60 ± 0.1[‡]
Ti	Healthy	0.81 ± 0.1	0.62 ± 0.1[*]	0.64 ± 0.2	0.64 ± 0.1
	Asthma	0.80 ± 0.2	0.61 ± 0.1[*]	0.72 ± 0.1	0.65 ± 0.1
Rrs I	Healthy	0.87 ± 0.2	0.66 ± 0.2[*]	0.71 ± 0.1	0.70 ± 0.2[‡]
	Asthma	0.83 ± 0.2	0.68 ± 0.1[*]	0.87 ± 0.1	0.75 ± 0.1[‡]

^{*} NREM < Wake, p < 0.05[‡] NREM < REM, p < 0.05