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Lung
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Overnight Changes in Lung Function of Obese Patients with Obstructive Sleep Apnoea

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Abstract
Purpose Obstructive sleep apnoea (OSA) is a prevalent disorder, characterised by collapse of the upper airways during sleep. The impact of sleep-disordered breathing on pulmonary function indices is however currently not well described. The aim of the study was to evaluate diurnal change in lung function indices in a cohort of patients with OSA and relate pulmonary function changes to disease severity.
Methods 42 patients with OSA and 73 healthy control subjects participated in the study. Asthma and COPD were excluded in all volunteers following a clinical and spirometric assessment. Spirometry was then performed in all subjects in the evening and the morning following a polysomnography study.
Results There was no difference in evening or morning FEV_1 or FVC between patients and control subjects ($p > 0.05$). Neither FEV_1 nor FVC changed in control subjects overnight ($p > 0.05$). In contrast, FEV_1 significantly increased from evening (2.18/1.54–4.46/L) to morning measurement (2.26/1.42–4.63/L) in OSA without any change in FVC. The FEV_1 increase in OSA was related to male gender, obesity and the lack of treatment with statins or β-blockers (all $p < 0.05$). A tendency for a direct correlation was apparent between overnight FEV_1 change and RDI ($p = 0.05$, $r = 0.30$).
Conclusions Diurnal variations in spirometric indices occur in patients with OSA and FEV_1 appears to increase in subjects with OSA overnight. These changes occur in the absence of change in FVC and are directly related to the severity of OSA. These findings dictate a need to consider time of lung function measurement.

Keywords Forced expiratory volume in 1 s · Lung function · Obstructive sleep apnoea · Overnight changes

Introduction

Obstructive sleep apnoea (OSA) is a common disorder which is characterised by intermittent complete or partial collapse of the upper airways during sleep. This results in overnight hypoxaemia and frequent arousals which may lead to excessive daytime sleepiness and the development or worsening of metabolic, cardiovascular and cognitive disorders [1].

OSA is a disorder which not only affects the upper airways but can also impact on the intra-thoracic airways. Indeed, reduced lung volumes, decreased elasticity and increased resistance of the lower airways are associated with more severe disease [2–5]. In addition, chronic airway diseases, including asthma and chronic obstructive pulmonary disease (COPD), influence the course of OSA [6, 7]. Lower airway inflammation and oxidative stress are accelerated in OSA with a direct relationship between disease severity and the magnitude of lower airways inflammation [8]. It appears likely that OSA may also impact on lung volume mechanics.

To date, however there have been no studies evaluating overnight alterations in lung function indices in OSA. Theoretically, lung function may vary due to two

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main reasons. On one hand, overnight changes in airway broncho-reactive mediator concentrations were reported and may influence operational lung volumes [8–12]. On the other hand, OSA is associated with increased sympathetic and decreased parasympathetic tone during sleep, especially during apnoeic periods [13–15], which may result in alterations in resting bronchial tone [16–18].

The aim of the study was therefore to evaluate diurnal change in lung function indices in a cohort of patients with OSA and compare these with a healthy control cohort. Apart from providing improved understanding regarding pathophysiology in OSA, this evaluation has important clinical implications, namely when to perform lung function testing in patients with OSA.

Methods

Study Subjects and Design

115 adult volunteers were recruited (47 men, 51 ± 15 years, BMI 27.1 ± 5.8 kg/m^2). COPD and asthma were excluded by spirometry and rigorous assessment of medical history in all subjects. More specifically, we excluded patients if any of the evening or morning FEV_1/FVC ratio was below 0.70, or if they reported chronic or intermittent symptoms of wheezing, shortness of breath, chest tightness and cough. However, no bronchial provocation or bronchial reversibility test has been performed. Subjects who could not perform reliable and reproducible lung function tests were excluded. Subjects were recruited from patients attending Sleep Laboratory of Semmelweis University, Department of Pulmonology ($N = 32$), and through internet advertisement ($N = 83$), and none of them has previously been diagnosed with sleep-disordered breathing. Accordingly, no subject had used continuous positive airway pressure (CPAP) device prior to recruitment. Thirteen patients were current or ex-smokers, 42 subjects were previously diagnosed with hypertension, 15 had known diabetes, 28 had dyslipidaemia and 26 had allergic rhinitis. None of the subjects had respiratory tract infection 1 month prior to the study.

Medical history was taken, patients filled in the Epworth Sleepiness Scale, blood pressure and heart rate were measured and lung function tests were performed in the evening (between 7 and 8 pm). Subjects then attended a full-night polysomnography. Blood pressure and heart rate were measured and lung function tests were repeated between 7 and 8 am, within an hour after awakening. The study was approved by the local ethics committee (Semmelweis University TUKEB 30/2014) and volunteers gave their written informed consent.

Polysomnography

Polysomnography was performed as described previously [9] using Somnoscreen Plus Tele PSG (Somnomedics GmbH, Germany) according to the guidelines [19]. Apnoea–hypopnoea index (AHI), respiratory disturbance index (RDI) and oxygen desaturation index (ODI) were recorded and used as indices for OSA severity.

Spirometry and Blood Pressure Measurement

Spirometry was performed with the Otthon device (Thor Medical Systems, Budapest, Hungary) according to the European Respiratory Society guidelines [20]. At least three technically acceptable lung function measurements were performed (the difference between the two highest values for forced vital capacity (FVC) or forced expiratory volume in one second (FEV_1) was <0.150 L). The highest values of FEV_1 and FVC were recorded. Blood pressure was taken using a mercury sphygmomanometer with cuff placed on the left upper arm.

Statistical Analysis

GraphPad Prism 5.0 (GraphPad Software, San Diego, CA, US) and Statistica 12 (StatSoft, Inc., Tulsa, OK, US) were used for statistical analyses. Data distribution was assessed with Kolmogorov–Smirnov test which showed a non-parametric distribution for FEV_1 and FVC, but parametric distribution for FEV_1/FVC. Unpaired t test, Mann–Whitney and χ^2 tests were used to compare clinical variables between OSA and control groups. Evening-to-morning changes in lung function were evaluated with Wilcoxon test and were expressed as Δ = morning − evening value. The relationships between lung function values and clinical variables were assessed with Spearman's test. Multiple logistic regression was applied to analyse the effect of potential covariates for the relationship between lung function indices and OSA severity. A p value <0.05 was considered significant. Data are expressed as mean ± standard deviation and median/range/for parametric and non-parametric data, respectively.

Results

Subject Demographics and Comparison of OSA and Control Subjects

Forty-two subjects were diagnosed with OSA (AHI ≥ 5/h) and 73 volunteers were considered as controls (AHI < 5/h). Compared to control subjects, patients with OSA were more frequently male, older and had a greater BMI.

Patients also had an increased rate of comorbidities including hypertension and dyslipidaemia ($p < 0.05$). Twenty-three patients with OSA and thirteen controls were obese (BMI $\geq$ 30 kg/m^2). The proportion of restrictive lung disease (FVC as well as $FEV_1 < 80$ % pred. and $FEV_1/FVC > 0.70$) was similar in obese patients with OSA (61 %) and obese controls (46 %, $p = 0.39$). A higher number of patients with OSA were treated with statins, Ca channel blockers, angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB, $p < 0.01$); however, no difference was found in the frequency of β-blocker users ($p = 0.72$; Table 1). There was no difference in FEV_1, FVC or FEV_1/FVC between the two groups either when they were measured in the evening or in the morning (all $p > 0.05$; Table 2).

Table 2 Lung function values in the evening and morning

	OSA	Control	*p*
FEV_1 (L)			
Evening	2.18/1.54–4.46	2.75/1.45–5.81	0.12
Morning	2.26/1.42–4.63	2.77/1.52–5.61	0.19
p	0.02	0.74	
FVC (L)			
Evening	2.60/1.83–5.32	3.28/1.79–6.51	0.17
Morning	2.71/1.77–5.64	3.17/1.79–5.91	0.23
p	0.19	0.97	
FEV_1/FVC			
Evening	0.84 ± 0.05	0.85 ± 0.07	0.26
Morning	0.84 ± 0.06	0.86 ± 0.07	0.11
p	0.78	0.54	

Forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) values and FEV_1/FVC ratios in the evening and morning in patients with obstructive sleep apnoea (OSA) and control subjects. Data are expressed as median/range/for FEV_1 and FVC and as mean ± standard deviation for FEV_1/FVC

Relationship Between Spirometric Indices and Disease Severity in Patients with OSA

There was an indirect relationship between FEV_1 measured in the evening (expressed as % predicted) and AHI ($p = 0.02$, $r = -0.34$), ODI ($p = 0.02$, $r = -0.35$) as well as RDI ($p = 0.01$, $r = -0.39$). Similarly, evening FVC (% predicted) was associated with AHI ($p = 0.04$, $r = -0.31$; Fig. 1), ODI ($p = 0.04$, $r = -0.31$) and RDI ($p < 0.01$, $r = -0.39$). FEV_1 in the morning (% predicted) was inversely related to RDI ($p = 0.03$, $r = -0.33$), and morning FVC values (% predicted) were negatively associated with AHI ($p = 0.03$, $r = -0.33$) and RDI ($p = 0.01$, $r = -0.38$). Neither FEV_1/FVC ratio nor absolute lung volumes were related to OSA parameters. In

Table 1 Comparison of clinical variables of study participants

	OSA	Control	*p*
Age (years)	64/36–74	46/20–74	<0.01
Gender (male/female)	23/19	24/49	0.02
BMI (kg/m^2)	31.1 ± 6.3	24.8 ± 4.0	<0.01
Hypertension (*n*)	25/17	17/56	<0.01
Diabetes (*n*)	8/34	7/66	0.14
Dyslipidaemia (*n*)	19/23	9/64	<0.01
Allergic rhinitis (*n*)	6/36	20/53	0.09
Medication usage (yes/no)			
Statins	11/31	1/72	<0.01
Ca channel blockers	8/34	2/71	<0.01
ACEI or ARB	14/28	7/66	<0.01
B-blockers	8/34	12/61	0.72
Smoking history (ever/never smoker)	5/37	8/65	0.87
Cigarette pack years	0/0–30	0/0–33	0.16
Epworth sleepiness scale	5/0–14	6/0–14	0.10
AHI (1/h)	17.0/5.2–93.3	0.9/0.0–4.8	<0.01
ODI (1/h)	18.8/0.0–119.4	1.0/0.0–18.3	<0.01
RDI (1/h)	27.0/14.2–103.5	10.5/0.6–24.2	<0.01

Significant differences were observed in age, gender, body mass index (BMI), prevalence of hypertension, dyslipidaemia, statin, Ca channel blocker as well as angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) treatment, apnoea–hypopnoea index (AHI), oxygen desaturation index (ODI) and respiratory disturbance index (RDI). Data are expressed as mean ± standard deviation for parametric or median/range/for non-parametric data

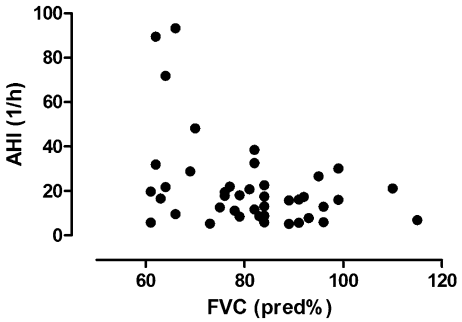

Fig. 1 Relationship between forced vital capacity and apnoea–hypopnoea index in OSA. There was a significant relationship between apnoea–hypopnoea index (AHI) and forced vital capacity (FVC) in OSA measured in the evening ($p = 0.04$, $r = -0.31$)

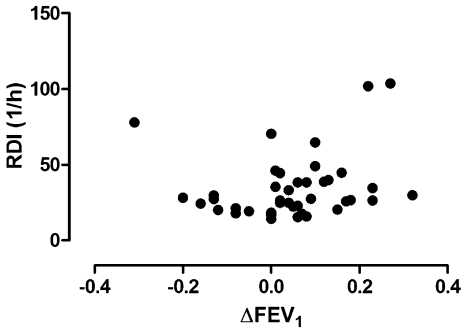

Fig. 2 Relationship between overnight FEV_1 change and respiratory disturbance index in OSA. There was a tendency for a direct relationship between respiratory disturbance index (RDI) and overnight changes in forced expiratory volume in 1 s in OSA ($p = 0.05$, $r = 0.30$)

addition, no correlation was observed between lung function and Epworth Sleepiness Scale ($p > 0.05$).

To assess the effect of potential covariates (age, gender, obesity, comorbidities, medication usage and smoking) on the relationship between lung function and OSA severity, the OSA group was divided into mild (AHI 5–14.9 1/h, $n = 17$), moderate (AHI 15–29.9 1/h, $n = 17$) and severe (AHI > 30 1/h, $n = 8$) subgroups. Multiple logistic regression revealed BMI, hypertension, diabetes, dyslipidaemia as well as treatment with statin, ACEI, ARB and β-blocker as significant covariates (all $p < 0.05$). In contrast, age, gender, smoking, allergy and therapy with a Ca channel blocker did not contribute to the relationship (all $p > 0.05$).

Overnight Changes in Spirometric Indices

In OSA, there was a significant increase in FEV_1 from the evening to the morning ($p = 0.02$), while no difference in FVC ($p = 0.19$) or FEV_1/FVC ($p = 0.78$) was noted. Morning and evening FEV_1 ($p = 0.74$), FVC ($p = 0.97$) or FEV_1/FVC ($p = 0.54$; Table 2) were not different in the control group. Analysing factors associated with lung function changes in OSA, significant relationships were observed between ΔFEV_1 and height ($p = 0.02$, $r = 0.35$), smoking status ($p < 0.01$, $r = -0.44$) and cigarette pack years ($p < 0.01$, $r = -0.44$), and a tendency for a positive correlation with RDI ($p = 0.05$, $r = 0.30$; Fig. 2) was also noted. No correlation was observed between changes in lung function and Epworth Sleepiness Scale ($p > 0.05$). With respect to the effect of gender, a significant FEV_1 change was observed only in males ($p = 0.03$), but not in females ($p = 0.25$). In addition, FEV_1 increased only in patients with OSA not using statins ($p = 0.02$) or β-blockers ($p = 0.03$), while there was no change in patients on treatment with statins ($p = 0.97$) or β-blockers ($p = 0.54$). Ca channel blocker, ACEI or ARB therapy did not affect the results. When the OSA group was divided into obese ($n = 23$) and non-obese subgroups ($n = 19$), a significant FEV_1 increase was found only in obese patients ($p = 0.03$), while no difference was observed in non-obese subjects ($p = 0.33$). In contrast, there was no change either in the thirteen obese ($p = 0.90$) or non-obese ($p = 0.63$) controls.

Overnight Changes in Blood Pressure and Heart Rate

In OSA, there was no overnight change either in systolic (evening to morning: 140/100–190 to 140/110–190 mmHg, $p = 0.97$) or diastolic (80/70–120 to 85/60–120 mmHg, $p = 0.97$) blood pressure values. However, heart rate increased in the morning (74/56–91 to 79/60–94/1/min, $p = 0.01$). In contrast, a significant drop in morning systolic (125/90–170 to 120/100–160 mmHg, $p < 0.01$) and diastolic (80/65–110 to 75/60–100 mmHg, $p < 0.01$) blood pressure was observed in control subjects with no change in heart rate (from 76/44–96 to 76/51–97/1/min, $p = 0.24$). Neither absolute values nor changes in blood pressure or heart rate were related to lung function indices or their overnight changes (all $p > 0.05$).

Discussion

OSA is a common disorder with an unclear pathophysiology. Despite the fact that the first report on the association between lung volumes and OSA was published already 30 years ago [3], changes in the behaviour of the intrathoracic airways have not been investigated in this disorder. Our study was the first to demonstrate diurnal change in select lung function parameters in a cohort of well-characterised patients with OSA with pathophysiological and clinical implications. We found a significant 80-mL overnight increase in FEV_1 in patients with OSA which directly related to the overnight apnoeic burden.

A reduction in end-tidal lung volumes may lead to a heightened potential for collapse of the upper airways [5]. Indeed, the relationship between reduced lung volume, increased respiratory resistance and increased severity of OSA is already described [2–4]. In keeping with these studies, we also found a significant, albeit weak association between spirometric indices and OSA severity. Although obesity may lead to restrictive ventilatory defect, there is a growing body of evidence linking OSA to impaired lung function; necessitating the investigation of sleep-disordered breathing in patients with restrictive parenchymal lung diseases.

Interestingly, a significant inverse relationship was also observed between changes in lung function indices and smoking status. Smoking even without COPD is associated with impaired respiratory mechanics [21]. Our study suggests that smoking non-COPD OSA patients are prone to develop overnight fall in FEV_1, a feature known in chronic respiratory diseases [22].

The reasons for the alterations in lung function observed in the current study remain to be determined. Changes in lung function potentially result from nocturnal release of broncho-reactive mediators. Overnight increase in the levels of potentially bronchoconstrictive 8-isoprostane [10] and bronchodilator nitric oxide [11, 12] has previously been reported in the exhaled breath samples in OSA subjects and these mediator changes may be responsible for the findings reported in the current study. Another possible explanation is the augmented adrenal-sympathetic tone during the night in OSA patients [13, 14, 23]. Although bronchi are innervated by parasympathetic rather than sympathetic nerves in mammals [16, 18], circulating adrenalin is a potent bronchodilator in humans [17]. During apnoeic periods, parasympathetic tone is decreased [24] and repeated arousal stimuli are associated with increased sympathetic activity [25], which may also lead to bronchodilation. This imbalance between sympathetic and parasympathetic tone may last even during wakefulness [15, 26]. In the current study, this fact was supported by the lack of physiological blood pressure dip and the increase in heart rate. Although we did not measure circulating catecholamines, previous studies report an increase in the concentration of blood adrenaline overnight in OSA [23] and this may contribute to a propensity to bronchodilation [27].

Not surprisingly, we found significant differences in age, gender, BMI, the prevalence of comorbidities and medications between patients and controls. Age did not influence our results; however, FEV_1 increased only in male patients. The precise explanation for our findings is not known, but there are certain gender differences in the distribution of adipose tissue, upper airway anatomy, control of ventilation and release of hormones [28]. We found that BMI was a covariate for the relationship of lung function and OSA severity. In addition, significant evening-to-morning increase in FEV_1 was present only in obese patients with OSA. Obesity may lead to the development of airway hyper-responsiveness both in animals and humans [29]. The underlying mechanisms include both mechanical (increased abdominal and chest wall mass as well as shallow breathing) and humoral (circulating inflammatory cytokines and hormones, such as leptin or adiponectin) factors [29]. However, obesity did not exclusively explain our findings, as no change in lung function was observed in obese non-OSA subjects.

Patients with OSA were more frequently treated with medications potentially affecting airway patency. We found that statin and β-blocker usage significantly blunted evening-to-morning FEV_1 elevation. It is known that chronic treatment with statins [30] and β-blockers [31] inhibits airway hyper-reactivity. Furthermore, the sympathetic blockade by β-blockers may contribute to the lack of FEV_1 changes. Of note, although gender, obesity and drug treatment modified our findings, this study was not powered to analyse causality of these factors. Therefore, these effects need to be investigated in further studies.

The limitations of this study include the relatively low sample size and the lack of objective measurement of bronchial hyper-reactivity. The sample size was estimated to find differences in lung function between the OSA and control groups. Although we reported that there were significant differences when the groups were divided according to gender, obesity and medication usage, the low sample size in the subgroups limits our ability to fully determine the influence of these factors.

Lung function exhibits some degree of diurnal variation in health and chronic airway diseases [22, 32]. It is known that patients with chronic airway disease other than asthma (i.e. COPD or allergic rhinitis) and even healthy subjects may show some degree of bronchial hyper-responsiveness [33], and obesity may itself predispose towards hyper-responsiveness without other symptoms of asthma [29]. As symptoms are imperative constituents of asthma definition, we believe that by rigorous assessment of medical history, bronchial asthma was reliably excluded. However, we did not perform bronchial reversibility or provocation test. Therefore, further studies are needed to evaluate airway hyper-responsiveness in obese OSA. Furthermore, as variability of lung function is well known even in healthy subjects, multiple evening-to-morning assessment would provide stronger evidence for our findings. Finally, although FEV_1 is more commonly used to assess airway obstruction than the measures of airway/respiratory resistance, independent studies using body plethysmography or forced oscillation technique would be highly informative in this context.

In conclusion, FEV_1 increased from evening to morning in patients with untreated OSA and the magnitude of this change was directly related to the severity of OSA. These findings may be explained by increased sympathetic tone or elevated levels of bronchodilator mediators caused by untreated sleep-disordered breathing. The significant increase in FEV_1 value in some patients (i.e. those with more severe OSA) may need to be taken into account when interpreting results of lung function tests. Further studies are needed to evaluate the mechanisms underlying these changes and their implications in patients with OSA.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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