Increased Exhalated Carbon Monoxide, Smoking and Obstructive Sleep Apnea

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Although exhaled carbon monoxide (CO) is studied from decades, a few studies are about its levels in smokers with obstructive sleep apnea (OSA). The average level of exhaled CO (eCO) was determined in OSA smokers and found increased significantly higher than in patients with other breathing related sleep disorders. A gender significant difference in average eCO was also noticed, with higher numbers in men, in OSA patients. A threshold of the eCO ≥ 6 ppm has 100% specificity and 96.3% sensitivity in detection of the active smoking habit in patients with OSA. Among OSA comorbidities, only chronic obstructive pulmonary disease (COPD) seams to influence the increased eCO levels in OSA active smokers.

Keywords: CO, smoking, obstructive sleep apnea, breathing related sleep disorders, COPD

Carbon monoxide (CO) in human body has both exogenous and endogenous sources. The exogenous source is represented mainly by smoking, but significant higher levels, although smaller than the ones in active smokers, were found in domestic exposure to gas-fired water heaters [1]. The vast majority of the endogenous CO is the end product of the hem metabolism and requires an active microsomal heme oxygenase. Proper expression of the induced heme oxygenase and a certain level of CO formation is hypothesized to protect the lung from external aggression [2]. Some studies have shown that CO plays a role in the protection against lung inflammation and injury. Healthy smokers, for example, had higher values of eCO than nonhealthy smokers [3]. Although CO is considered a biomarker of oxidative stress, many unknown features about the action of this gaz in lung diseases are to be solved especially in patients with obstructive sleep apneea [4-6]. Experimental studies have shown a supressive role of CO on the pro-inflammatory citokines (TNFα- tumor necrosis factor alpha; IL1β- interleukin 1 beta; MIP1β- macrophage inflammatory protein-1 beta) and an increasement of the anti-inflammatory ones (IL10- interleukin-10) [7]. A positive anti-inflammatory effect was found in low dose inhalation of CO in COPD patients [2]. By now, contradictory results of breathing CO have been reported in chronic lung diseases attempting to include the CO level on the inflammatory biomarkers list [8-10]. Measuring eCO is a widely used method in monitoring smoking cessation programs. The eCO level is influenced by the speed [11] and the phase of exhalation [12]. The sleep-wake status has also an influence on the half time of CO, which is longer during sleep (4-8 h) than during daytime (2-3h) in normal individuals [13]. Breathing related sleep disorders (BRSD) might influence the accumulation of CO. As there are a few studies concerning the level of CO in smokers with breathing related sleep disorders, the aim of the study was to focus on the evaluation of the relationship between OSA and exhaled CO in active smokers.

Experimental part

The study included adults diagnosed with breathing related sleep disorders (BRSD) in a sleep laboratory who informed consented to be investigated. Cases were considered patients diagnosed with obstructive sleep apneea (OSA), having an apneea - hypopnea index (AHI) ≥ 5 obstructive or mixt (apneea and hypopnea) events / hour of sleep. The data base contained informations about smoking status, medical history, symptoms, clinical and paraclinical examination, including anthropometric indexes as body mass index (BMI), neck circumference (NC), waist circumference (WC) and eCO measurement. The procedure of BRSD diagnostic was the cardio-pulmonary poligraphy (STARDUST II RESPIRONICS), which recorded the nasal respiratory flow, the blood O_2 saturation, the cardiac frequency, the snoring, the body position and the respiratory effort during sleep. The validation of the diagnostics was based according to AASM definitions [14], updated in 2014 [15]. Other BRSD (nonOSA) consisted in upper airways resistance syndrome (UARR), considered if AHI <5/h, with no significant desaturation and minimal blood O_2 saturation (SpO_2) ≥ 92%; central sleep apnea, diagnosed if AHI≥5/h, consisted of central apnea of hypopneas; and obesity-hypoventilation syndrome (OHS) defined by BMI ≥30 kg/m^2 with an average SpO_2 <90% in > 30% of the total duration of the sleep. BMI was calculated by dividing the weight to the square of the body height.

NC was measured in an horizontal plane below the thyroid cartilage, perpendicular to the long axis of the neck, while the WC was taken at the half distance between the last rib and the iliac crest, with a plastic tape measure. The measurement of eCO levels was assessed among cases with OSA versus patients with other BRSD (nonOSA), by Smokerlyzer (Bedfont Scientific Ltd.), an instrument that used an electrochemical sensor to analyse the exhaled air concentration of CO in the initial phase of expiration, when flow is maximal. Any patient must perform a sustained exhalation keeping a breathhold of 15 seconds and the limit of eCO detection is 1 ppm [12]. A threshold of eCO in the differentiation the active smokers from non smokers

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(or exsmokers) was calculated in cases. Statistical analysis was performed using an SPSS software (StatPlus:mac Pro, v6, 2018). OneWay ANOVA test wa used for parametrical variables, Mann-Whitney U and median test for the nonparametrical ones, Pearson correlation for normaly distributed variables and Spearman corelation for the ones that did not show normal distribution. A significance thereshold of 95% was considered for significant.

Results and discussions

From a total population of 306 patients mean aged 53.15+11.47 years, referred to a sleep medicine outpatient center placed in Constanta, Romania, and diagnosed with BRSD, more than a half were identified with obstructive sleep apnea (n=204; 66.66%). The distribution of 102 non OSA patients included other BRSD (10 cases of central sleep apnea, 14 with obesity hypoventilation syndrome and 78 with upper airways resistance syndrome). The majority of nonOSA patients were males (n=222/306; 72.54%) without differences among groups (OSA versus nonOSA), although the proportion of women was larger in nonOSA group (tabel 1). There were significant differences of distribution of cases by gender (p<0.002), smoking status and levels of eCO measurements (table 1).

Females were older than males (57.55 years +10.06 SD versus 51.76 years + 11.28; F=16.987, p=0.0005), with 78% of cases in the 6th and 7th decade of age compared to males who had a normal distribution. Anthropological measurements NC and WC measured in centimeters revealed significant differences of NC by gender (44.15cm ± 3.08 SD in men versus 40.48 cm ± 3.20 SD in women, p=0.000), according to the decades of age (F=2.637; p=0.024), and significant correlations of CG values with the number of sleep apneas (r= -0.207; p=0.000), nocturia (r= -0.207; p=0.000) and daytime sleepiness (r= -0.275; p=0.000). The mean value of WC was 108.56 cm ± 10.358, with no influence by age (F=1.981; p=0.081) but significantly higher in males compare to females women [109.89 cm ± 9.80 SD versus 105.03 cm ± 11.01 SD. WC; F=14.831; p=0.000). WC was corellated to apneas (r= -0.208; p=0.000), nocturia (r= -0.178; p=0.001) and day sleepiness (r= -0.346; p=0.000). BMI was slightly higher in women than men (34.34 kg/m^2 ± 7.14 DS and men 33.51kg/m^2 ± 6.26 DS; F=1.060; p=0.304), significantly correlated with nocturia (r= -0.182; p=0.001), dyspnoea (r= -0.168; p=0.002) and diurnal sleepiness (r=-0.301; p=0,000). Overall, all anthropometric measures are in relatioship with OSA patients' symptoms.

Smoking status of patients was quite similar in both groups (p >0.05) (table 1), with slightly more active smokers (39.7%) in OSA group.

Average eCO was higher in OSA cases (U= 11871.5, p=0.044) (fig. 1).

A possible confounder might be considered the significant difference of BMI among OSA versus nonOSA patients. An increased activity of heme oxygenase, with elevated levels of eCO, has been described in obese patients as a protective mechanism against inflammation [16]. However, in our study, there was no correlation between BMI and eCo neither in the study group (F=2.103, p=0.141), nor in OSA (F=1.629, p=0.20) or nonOSA (F=2.647, p=0.106) subgroups; therefore, it is not likely

Characteristics	Total BRSD (mean ± SD)	OSA (mean + SD)	nonOSA (mean + SD)	P
Patients (nr; %)	306	204 (66.7%)	102 (33.3%)	
Age (years)	53.15±11.47	52.84 ±10.61	54.36±12.41	0.2657
Gender (M/F)	222/84	160/44	62/40	0.0011
NC (cm)	43.15 ± 3.51	44 ± 3.45	41.67 ± 3.14	0.0000
WC (cm)	108.56 ± 10.36	111.71 ± 10.29	103.43 ± 8.42	0.0000
BMI (kg/m^2)	33.73 ± 6.5	35.21 ± 6.71	31.62 ± 5.5	0.5525
Active Smokers	115	81	34	0.0000
Never Smokers	102	66	36	0.0000
Former Smokers	89	57	32	0.0000
eCO (ppm)	8.14 ± 9.92	9.10 ± 10.64	6.25 ± 7.99	0.017

Legend: OSA = obstructive sleep apnea; BRSD = breathing related sleep disorders; NC = neck circumference; WC = waist circumference; BMI = body mass index; eCO = exhaled CO; M= male; F = female; SD = standard deviation

Table 1
DESCRIPTIVE STATISTICS OF STUDY GROUP

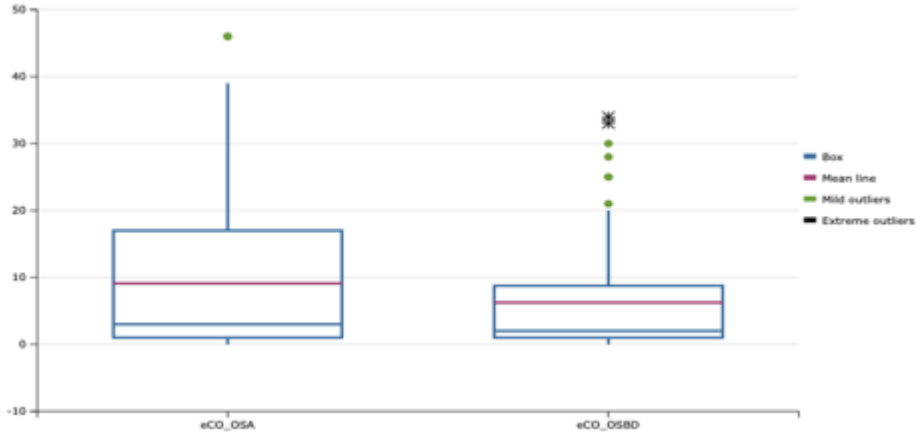

Fig. 1. The levels of exhaled CO in obstructive sleep apnea patients (OSA) compare to cases with other breathing related sleep disorders (nonOSA)

Table 2
AVERAGE eCO LEVELS IN ACTIVE SMOKERS ACCORDING TO THE COMORBIDITIES OF THE BREATHING RELATED SLEEP DISORDERS

Comorbidities	OSA active smokers		nonOSA active smokers	
	Number	eCO (ppm) Mean+ SD	Number	eCO (ppm) Mean+ SD
Obstructive lung diseases	Yes (n=34)	22.88±11.01*	Yes (n=13)	15.46 ±8.51
	No (n=47)	17.81±7.29	No (n=21)	15.28 ±8.95
COPD	Yes (n=31)	23.61±10.84*	Yes (n=9)	16.22 ± 6.77
	No (n=50)	17.66 ± 7.49	No (n=25)	15.04 ± 8.52
Asthma	Yes (n=4)	16.25 ± 10.01	Yes (n=5)	14.2 ± 5.81
	No (n=77)	20.13 ± 9.32	No (n=29)	15.55 ± 8.39
Cardiovascular diseases	Yes (n=45)	18.82 ± 8.74	Yes (n=11)	16 ±7.16
	No (n=36)	21.33 ± 9.95	No (n=23)	15.04 ± 8.52
Cerebrovascular diseases	Yes (n=1)	22	Yes (n=2)	15.5 ± 0.71
	No (n=80)	19.91 ± 9.37	No (n=32)	15.34 ± 8.26
Metabolic syndrome	Yes (n=11)	22.82 ± 11.48	Yes (n=5)	17.8 ± 8.29
	No (n=70)	19.49 ± 8.95	No (n=29)	14.93 ± 8.03
Type 2 diabetes	Yes (n=13)	23.15±10.59	Yes (n=7)	17 ± 6.93
	No (n=68)	19.32 ± 9.02	No (n=27)	14.92 ± 8.33
Other endocrinological diseases	Yes (n=2)	8,00±2,82	Yes (n=3)	9.66 ± 5.86
	No (n=79)	20,24±9,23	No (n=31)	15.9 ± 8.04
Ear Nose Throat diseases	Yes (n=24)	20.29 ± 9.05	Yes (n=6)	13.83 ± 7.70
	No (n=57)	19.79 ± 9.51	No (n=28)	15.67 ± 8.17
Psychiatric diseases	Yes (n=1)	13	Yes (n=5)	23.8 ± 10.06
	No (n=80)	20.03 ± 9.34	No (n=29)	13.89 ± 6.79

that BMI is interfering this result. Another potential factor of influence could be the gender distribution, as women has generally lower muscle mass and myoglobin to bind CO, or the elimination rate of CO is lower in men [17]. On the other side, loss of muscle mass and functionality is frequent in OSA [18] and might counterbalance this effect. Men were, proportionally, more in the OSA group and significant difference was found between eCO increased levels in men with BRSD versus women (9.32 mean, 4 median value in men versus 5.06 mean, 2 median in women; U= 11113.5; p=0.0096), but these differences were not reproduced within subgroups (U= 4140, p=0.074 in OSA and U=1447.5, p=0.155 in nonOSA).

Active smokers represented 37.58% of BRSD patients (n=115/306), and the majority of them were diagnosed with OSA (n= 81/115; 70.43%). The average of eCO levels was higher in OSA (19.94 ppm ± 9.32 SD) versus nonOSA patients (15.35 ppm ± 8.01 SD; F=6.274; p=0.014), with significant increased levels in OSA active smokers, by gender (men had higher eCO: 21.09 ppm ± 9.26 SD versus women: 13.92 ppm±7.35 SD; F=6.924; p=0.010). In OSA patients, active smoking had a 100% specificity (n=66/66) and the highest sensitivity (96.3%, n=78/81) at a threshold value of the eCO ≥ 6 ppm. Up to date, there was no specific threshold described for the defining active smokers in OSA. It is estimated that a normal level of eCO for a non smoker is 4 ppm and a value of 7 ppm would mark the line between the smokers and the non-smokers [20], although other researchers have found a wider range, from 6 [18] to 10 ppm [21]. The threshold level for eCO found in this study is very important for two reasons: firstly, because it is not a general threshold, but a specific one for OSA patients and, secondly, because all OSA patients should be included in smoking cessation programs, particularly if they might be at risk during their current occupation [22]. Finnally, the levels of eCO were evaluated in relation with the main comorbidities of OSA (table 2), which might have an influence on the symtoms and the overall quality of life in lung patients [23]. The mean value of eCO was significantly increased in OSA patients, active smokers, with associated COPD [24]. All other comorbidities added no supllementary differentiation among the patients' groups.

Conclusions

In this research, eCO distinguishes patients with OSA from other breathing related sleep disorders nonOSA. Male gender and COPD overlapping OSA are the risk factors of increased eCO levels in smokers. A threshold of eCO≥6 ppm could be asigned for the identification of the active smokers among OSA patients.

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