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Risk factors and fraction of exhaled nitric oxide in obstructive sleep apnea in adults

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Abstract

Objective: This study aimed to evaluate the relationship between obstructive sleep apnea (OSA) and the fraction of exhaled nitric oxide (F_{ENO}), and to assess the effect of risk factors of airway inflammation on OSA.

Methods: Medical records of patients in the Respiratory Sleep Center at Chao-Yang Hospital in Beijing between January 2015 and June 2017 were analyzed. All patients were diagnosed with OSA. Data of the medical history, clinical examinations, F_{ENO}, and upper airway computed tomographic findings were collected. Logistic regression was used to evaluate risk factors of OSA.

Results: A total of 181 patients were admitted to the Respiratory Sleep Center during the study and 170 had a diagnosis of OSA and were included in the study. Single factor analysis showed that male sex, age, body mass index, smoking index, alcohol consumption, F_{ENO}, soft palate thickness, soft palate length, the narrowest transverse diameter of the upper airway, tonsil size, and nasal sinusitis were risk factors for sleep-disordered breathing and disease severity.

Conclusions: Male sex, age, body mass index, F_{ENO}, the narrowest transverse diameter of the upper airway, and normal tonsil size are associated with OSA and disease severity. The severity of OSA is associated with F_{ENO} levels.

Keywords

Obstructive sleep apnea, risk factor, nitric oxide, upper airway computed tomography, inflammation, sleep-disordered breathing

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Introduction

Obstructive sleep apnea (OSA) is a breathing disorder disease, which causes temporary cessation of airflow for 10 s while continuing ventilation during patients' sleeping.[1] OSA is present in 4% of men and in 2% of women. Intermittent arterial oxygen desaturation, nocturnal arousal, and sleep disorders occur after a recurrent obstructive upper airway.[2] Previous studies have shown several risk factors of OSA, and these contribute to prevention and management of OSA.[3]

Nitric oxide (NO) is produced in the presence of inducible NO synthase enzyme within airway cells and is implicated in the pathogenesis of inflammation of the airway in some respiratory diseases.[4] NO is easily, reliably, and noninvasively measured from exhaled breath. The fraction of exhaled NO (F_{ENO}) plays an important role in the airway compartment.[5] In theory, drug therapy directed at alleviating inflammation might be a possible approach for treating OSA. However, over the last 20 years, several studies that measured levels of F_{ENO} in patients with OSA reported contradictory results, including increased, comparable, or decreased F_{ENO} levels in patients with OSA compared with healthy patients.[6]

The overall purpose of our study was to describe the role of not only risk factors, but also upper airway structure parameters and levels of inflammatory markers in patients with OSA. Therefore, the primary aim of our study was to assess the potential association between OSA and F_{ENO} levels. Our secondary aim was to review the effect of airway inflammation on occurrence and development of OSA. Additionally, we aimed to assess and rank the risk factors for OSA using an ordinal logistic regression model.

Methods

Research design

Medical records of patients who were admitted to the Respiratory Sleep Center at Chao-Yang Hospital in Beijing, affiliated to Capital Medical University between January 2015 and June 2017 were analyzed. All included patients who were diagnosed with OSA. The following data were collected for all patients who were diagnosed with OSA: medical history, clinical examination results, F_{ENO}, and upper airway computed tomographic (UACT) findings. We performed a prospective analysis in the current study.

Patients

This study contained patients who had sleep-disordered breathing (SDB). This study only included patients who had been diagnosed with OSA when the apnea–hypopnea index was $\geq$5 based on a polysomnographic study.

Some characteristics of typical clinical symptoms of OSA were snoring, witnessed apneas, and excessive daytime sleepiness based on International Criteria of Sleep Disorders. Patients who had severe pulmonary, neurological, or cardiovascular disorders, or mental illness were excluded.

Determination of NO content

A portable electrochemistry-based machine (NObreath; Bedfont Scientific Ltd., Rochester, Kent, UK) was used to detect F_{ENO} before polysomnography on the basis of guidelines of the American Thoracic Society/European Respiratory Society.[7] Subjects had F_{ENO} detected, which required breathing for 10 s under a situation of constant flow (50 mL/s) and pressure (10 cm H_2O). At least two

acceptable measures were selected after repeatedly determining F_{ENO} differences <4 parts per billion. The average value of two measures was used as the result. Patients were required to avoid severe activity, such as taking the stairs and lifting weights, or having a big meal before an hour of examination.

UACT

All patients had three-dimensional UACT performed while staying awake at the end of exhalation with a high-speed 64-channel spiral computed tomographic (CT) scanner (Brilliance 64; Philips, Cleveland, OH, USA). Patients lay in the supine position and one axial scan was conducted at every 0.67 mm from the basis cranii to the vocal cords. Performance of CT imaging and interpretation of images were accomplished by the same person to assure the repeatability of the test. The first step was constructing CT imaging and rebuilding upper airway volume using axial images. The upper airway included the velopharynx, nasopharynx, and laryngopharynx. The following information was obtained from three different axial images: soft palate thickness, soft palate length, the narrowest anteroposterior diameter of the upper airway, the narrowest transverse diameter of the upper airway, nasal septum deviation, and nasal sinusitis.

Polysomnography

Polysomnography was used to diagnosis OSA.[8–10] This procedure included reports, electrocardiography, omental and pretibial electromyography, electro-oculography, electroencephalography, arterial oxygen saturation (SaO_2) of oral and nasal respiration, and chest movement. An integrated top airflow for at least 10 seconds was defined as an episode of apnea. In this situation, shallow and slow breathing reduced nasal pressure signals by 50% or 30% to 50%, and SaO_2 or electroencephalographic excitation was decreased by 3%. The apnea–hypopnea index (AHI) was defined as the total number of apnea and hypopnea events per hour of sleep, including obstructive or mixed apnea plus obstructive hypopnea. The respiratory disturbance index was defined as the total number of respiratory events per hour of sleep (total polysomnography) or per hour of sleep (polysomnography without electroencephalography). Apnea and hypopnea lasted at least 10 s and sleep apnea was defined as an AHI of $\geq$5 events.

Statistical analysis

The data are expressed as mean $\pm$ standard deviation. All experiments were repeated at least three times and the data were analyzed using SPSS software version 22.0 (IBM, Armonk, NY, USA). All results were analyzed with the chi-square test or Fisher's exact test. $P<0.05$ was considered to indicate a statistically significant difference.

Ethical agreement

Our research protocol was approved by the Scientific Research and Technology Ethics Committee of Beijing Chao Yang Hospital. Formal consent was not required for this type of study.

Results

Subjects

A total of 181 patients were admitted to the Respiratory Sleep Center with SDB during the study period. Of these, 170 had a diagnosis of OSA and were selected for this study (mean age $\pm$ standard deviation, 43 ± 11.8 years; 77.9% men).

Table 1. Sleep respiratory parameters of sleep-disordered breathing in this study.

	Snoring (AHI <5)	Mild OSA (AHI ≥5 and <15)	Moderate–severe OSA (AHI ≥15)	P value
AHI	3.23±0.92	15.43±5.65	58.61±17.72	<0.001
ODI	3.10 (1.87–3.70)	14.30 (12.73–15.26)	56.00 (50.68–58.47)	<0.001
SaO_2 (%)	95.9 (94.14–96.63)	93.90 (93.72–94.39)	91.50 (89.69–91.25)	<0.001
Minimum SaO_2 (%)	89.36±3.38	83.69±4.74	69.43±9.49	<0.001
Drop in desaturation	3.05±1.07	4.62±1.07	10.07±4.60	<0.001

Values are mean ± standard deviation or median (range). OSA, obstructive sleep apnea; AHI, apnea–hypopnea index; ODI, oxygen desaturation index; SaO_2, arterial oxygen saturation.

Baseline characteristics and polysomnography

All patients with SDB underwent polysomnography. Polysomnographic parameters, including the AHI, oxygen desaturation index, and mean drop in desaturation, significantly increased with disease severity (all $P < 0.001$). Additionally, mean SaO_2 and minimum SaO_2 significantly decreased with disease severity (both $P < 0.001$) (Table 1).

Univariate analysis of demographic and other characteristics of the patients are shown in Table 2. Single factor analysis showed that male sex, age, BMI, the smoking index, alcohol consumption, F_{ENO}, thickness of the soft palate, length of the soft palate, the narrowest transverse diameter of the upper airway, tonsil size, and nasal sinusitis were possible risk factors for SDB in proportion to disease severity (all $P<0.05$). There was no a significant difference in the other characteristics (Table 2, Figure 1).

Ordinal logistic regression analysis of risk factors

The ordinal logistic regression model with 0.05 as the critical analysis was applied to identify risk factors for OSA according to disease severity (Table 3). We found that male sex, age, BMI, F_{ENO}, the narrowest transverse diameter of the upper airway, and tonsil size were associated with OSA (all $P<0.05$). The P value of goodness of fit test of this model was >0.05, which indicated a good fit. The parallel line test ($\chi^2 = 18.60$, $P = 0.01$) showed statistical significance. The coefficients of the respective variables in the model remained constant, regardless of the location of the splitting point of the response variable.

Relationship between F_{ENO} and upper airway inflammation based on UACT

All patients underwent UACT scans using a high-speed 64-channel spiral CT scanner at the end of expiration. Univariate analysis showed that F_{ENO}, soft palate thickness, soft palate length, upper airway stenosis, sinusitis, and upper airway stenosis were directly proportional to disease severity (all $P<0.05$).

Discussion

Our study mainly focused on risk factors and F_{ENO} in OSA in adults. We found that various factors, including male sex, age, BMI, the smoking index, alcohol consumption, F_{ENO}, soft palate thickness, soft palate length, upper airway stenosis, and sinusitis, were risk factors for SDB and disease severity.

Table 2. Demographic features and univariate analysis of variables associated with sleep-disordered breathing in this study.

	Snoring (AHI <5)	Mild OSA (AHI ≥5 and <15)	Moderate–severe OSA (AHI ≥15)	P value
Subjects, n	11	83	87	
Male/female	6/5	57/26	78/9	<0.001
Age, years	32.91 ± 7.60	43.41 ± 12.56	45.91 ± 10.84	<0.001
BMI (kg/m^2)	23.46 (21.47–27.04)	25.88 (25.42–26.87)	28.28 (28.10–29.52)	<0.001
GER, n	5/11	36/83	42/87	0.84
Smoking index	0.00 (−8.93–23.48)	0.00 (76.28–170.83)	0.00 (100.19–223.65)	0.04
Number of drinkers	1/11	21/83	39/87	<0.001
Allergic rhinitis, n	2/11	8/83	5/87	0.20
Familial history of snoring, n	2/11	20/83	22/87	1.00
Asthma, n	3/11	11/83	7/87	0.13
F_{ENO}	15.09 ± 4.50	23.33 ± 8.08	27.80 ± 6.86	<0.001
Thickness of the soft palate	9.53 ± 1.59	9.62 ± 2.08	10.89 ± 2.28	<0.001
Length of the soft palate	35.08 ± 3.63	37.99 ± 4.04	40.49 ± 5.31	<0.001
The narrowest anteroposterior diameter of the upper airway	8.73 ± 3.39	7.63 ± 2.18	7.83 ± 1.94	0.28
The narrowest transverse diameter of the upper airway	17.60 (15.13–20.74)	14.20 (14.19–16.52)	10.90 (10.38-11.99)	<0.001
Deviation of the nasal septum, n	6/11	37/83	36/87	0.72
Hypertrophy of nasal turbinates, n	5/11	26/83	28/87	0.67
Tonsil size, n	2/11	20/83	42/87	<0.001
Nasal sinusitis, n	3/11	41/83	58/87	0.01
ESS	11.00 (8.83–12.08)	10.00 (8.83–10.62)	11.00 (11.77–13.94)	<0.001

Values are mean ± standard deviation, median (range), or number. OSA, obstructive sleep apnea; AHI, apnea–hypopnea index; BMI, body mass index; GER, gastroesophageal reflux disease; F_{ENO}, fraction of exhaled nitric oxide; ESS, Epworth Sleepiness Scale.

Various factors increase susceptibility to OSA, including age, obesity, menopause, craniofacial deformity, male sex, family history of OSA, smoking, and drinking. Our study suggested that male sex, age, BMI, the smoking index, alcohol consumption, F_{ENO}, thickness of the soft palate, length of the soft palate, the narrowest transverse diameter of the upper airway, tonsil size, and nasal sinusitis were risk factors for OSA and might be associated with disease severity. To verify this observation, we further incorporated these risk factors into an ordinal model of logistic regression to evaluate the weight of individual risk factors of OSA. This model showed that age, male sex, BMI, F_{ENO}, the narrowest transverse diameter of the upper airway, and normal tonsil size were significantly associated with OSA and disease severity. Previous studies have shown a close relationship between increased age and occurrence of OSA.[11]

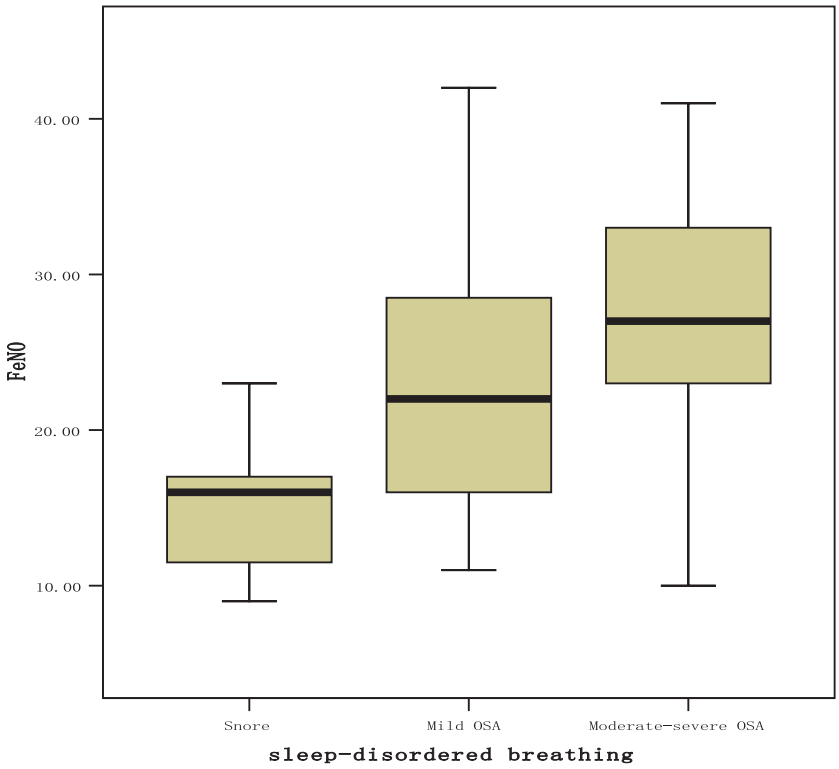

Figure 1. Increase in F_{ENO} in proportion to disease severity. F_{ENO}, fraction of exhaled nitric oxide.

Table 3. Ordinal logistic regression analysis of variables associated with sleep-disordered breathing in this study.

Parameter	Beta	Standard error	Odds ratio	P value
Male (female)	1.18	0.532	3.26	0.03
Age	0.08	0.02	1.08	<0.001
BMI	0.17	0.06	1.18	<0.001
Smoking index	−0.00	0.00	1.00	0.06
Number of drinkers	−0.37	0.43	0.69	0.40
F_{ENO}	0.09	0.02	1.09	<0.001
The narrowest transverse diameter of the upper airway	−0.19	0.04	0.83	<0.001
Normal tonsil size	−0.93	0.45	0.39	0.04

BMI, body mass index; F_{ENO}, fraction of exhaled nitric oxide.

In older people, the risk of OSA grows exponentially. These studies reported that the risk for OSA increases by 20% for each additional year (odds ratio = 1.20). This increased risk is attributed to age-related anatomical changes in the pharynx, which led to increased upper airway collapsibility.[12] There is a close relationship between increased BMI and a high risk of OSA.[13,14] Obesity causes narrowing of the

airway because of hyperadipose tissue in the neck. Neck circumference corrected by height has also been reported as a useful preventive factor of OSA. Some researchers have reported a relationship between OSA and male sex.[15,16] Susceptibility of men to OSA has been attributed to some factors, such as a difference in structure and function of the upper airway. Airway mechanics in women are much better than those in men. This difference in airway mechanics is due to more fat deposition around the airway of men compared with women, and a difference in hormones and clinical heterogeneity.[17] There are many various factors in the pathogenesis of OSA, such as anatomy and non-anatomical factors.[18] In recent years, the potential effect of some factors besides pharyngeal anatomy and craniofacial structure have been recognized in OSA. In our study, we found that anatomical factors, such as the thickness of the soft palate, the length of the soft palate, the narrowest transverse diameter of the upper airway, tonsil size, and nasal sinusitis, were closely associated with the severity of OSA.

We also found that increased F_{ENO} levels were related to upper airway inflammation in SDB and associated with disease severity. Airway and systemic inflammation have been suggested to play a crucial role in the pathophysiology of OSA.[19] Markers of inflammatory and oxidative stress in the lower airway of patients with OSA are increased. Previous studies have reported that F_{ENO} levels in patients with OSA and inflammatory metabolites were increased compared with those of healthy subjects.[20,21] Our study also showed that markers, such as age, male sex, BMI, the narrowest transverse diameter of the upper airway, normal tonsil size, and the level of F_{ENO}, were positively related to the severity of OSA. Elevated F_{ENO} levels in patients with OSA indicate the presence of inflammation in the bronchial and upper airway. Previous studies have shown the levels of polymorphonuclear cells and inflammatory mediators in the nasal mucosa of patients with OSA.[19,22] NO is the main factor of dependent vasodilatation, and its synthesis depends on the balance between occurrence and degradation of oxygen free radicals and oxidative free radicals.[23] Enhanced release of oxygen free radicals caused by hypoxia–reoxygenation exceeds the physiological antioxidant ability in OSA. This situation reduces the requirement for NO synthesis and leads to synthesis of more superoxide radicals and peroxynitrite.[24,25] Hypoxia can also change production of NO synthase in the vascular endothelium, reduce NO levels in the blood circulation, and adversely affect the vascular bed. As a physiological regulator of angiotensin, NO plays an important role as a pathological proinflammatory biomarker in many lung diseases. The theoretical basis of this role is that F_{ENO} may be affected by two major pathological processes in patients with OSA, namely pulmonary inflammation and endothelial dysfunction. NO can be easily detected in patients' breath. An increase in NO reflects pulmonary inflammation caused by overexpression of inducible NO synthase in asthma and systemic sclerosis.[26] Pulmonary inflammation and vascular injuries are usually concurrent in patients with OSA, but to varying degrees. F_{ENO} is either unchanged or increased in OSA, which reflects NO production from the large airways.[6,27]

Inflammation and endothelial dysfunction are two crucial characteristics of OSA.[28,29] Some studies have shown that increased exhaled NO has a close relationship with airway inflammation in patients with OSA. Upper airway inflammation has previously been shown by increased nasal NO levels.[18,30] There is a close relationship between over expression of inducible NO synthase and increased 3-nitrotyrosine in palatine tonsils of patients with OSA compared with healthy controls.

Furthermore, high F_{ENO} levels are associated with the severity of OSA, and they can induce more expression of NO synthase in sputum monocytes in patients with OSA.[27] Therefore, there is a close relationship between inflammatory markers and the severity of OSA, which can be useful for clinical monitoring of OSA. Recent studies reported that F_{ENO} levels were significantly increased in patients with OSA.[31,32]

The main limitation of this study is the retrospective study design. We acknowledge that there could be inaccuracies in the diagnoses and medical history recorded in the patients' records.

Conclusions

Some risk factors of OSA that were identified in our study are preventable. Knowledge of risk factors increases awareness, which contributes to making health care providers more sensitive to this burden, and could help provide a controlled strategy for preventing OSA. Our study shows that male sex, age, BMI, F_{ENO}, the narrowest transverse diameter of the upper airway, and normal tonsil size are associated with OSA and disease severity. The disease severity of OSA is associated with F_{ENO}. Theoretically, drug therapy directed at alleviating inflammation of the airway may be a novel possible approach for treatment of OSA. Therefore, future studies on these drug therapies are warranted. Furthermore, there is a need to further describe the interactions between OSA and upper airway inflammation from the view of pathophysiology.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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