นิพนธ์ต้นฉบับ • Original Article

ความสัมพันธ์ระหว่างการอักเสบของทางเดินหายใจกับความรุนแรงของภาวะหยุดหายใจขณะนอนหลับ

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Associations between Airway Inflammation and Indices of Sleep Apnea Severity in Obstructive Sleep Apnea Patients

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หลักการและวัตถุประสงค์: ภาวะหยุดหายใจขณะนอนหลับจากการอุดกั้น (Obstructive sleep apnea, OSA) เป็นกลุ่มอาการที่ซับซ้อนประกอบด้วย การอุดกั้นของทางเดินหายใจ ภาวะพร่องออกซิเจนชั่วคราว และ การนอนหลับที่ไม่ต่อเนื่อง จากการศึกษาที่ผ่านมาพบว่าภาวะพร่องออกซิเจนชั่วคราวนี้อาจมีความสัมพันธ์ต่อการอักเสบของทางเดินหายใจ ซึ่งการวัดปริมาณไนตริกออกไซด์ในลมหายใจออกเป็นวิธีหนึ่งที่สามารถใช้ประเมินการอักเสบของทางเดินหายใจ การศึกษาครั้งนี้มีวัตถุประสงค์เพื่อศึกษาความสัมพันธ์ระหว่างความรุนแรงของภาวะหยุดหายใจขณะนอนหลับจากการอุดกั้น กับการอักเสบของทางเดินหายใจ

วิธีการศึกษา: ศึกษากลุ่มผู้ป่วย OSA จำนวน 40 รายที่ได้รับการตรวจการนอนหลับและวินิจฉัยโดยแพทย์ผู้เชี่ยวชาญ และประเมินไนตริกออกไซด์จากลมหายใจออก ภายหลังจากการตรวจการนอนหลับ

ผลการศึกษา: พบว่า ดัชนีการหยุดหายใจและหายใจแผ่วเฉลี่ย 37.8 ± 5.8 /ชม. ดัชนีการตื่นเร้า 56.7 ± 14.5 /ชม. ดัชนีการหยุดหายใจ 19.0 ± 9.4 /ชม. ความอิ่มตัวของออกซิเจนต่ำสุดขณะนอนหลับ 87 ± 4% ระดับไนตริกออกไซด์ในลมหายใจออกเฉลี่ย 27.7 ± 2.2 ppb การอักเสบของทางเดินหายใจมีความสัมพันธ์กับระดับความรุนแรงของภาวะ

Background and Objectives: Obstructive sleep apnea (OSA) is a complex disorder that consists of recurrent upper airway collapse, intermittent hypoxia (IH), and sleep fragmentation. Previous studies suggest that IH may play a role in airway inflammation. Fractional exhaled nitric oxide (FeNO) levels have been used as markers for airway inflammation. This study investigated the association of sleep apnea severity with airway inflammation in patients with OSA.

Methods: Forty OSA patients diagnosed with medical specialists by the polysomnography (PSG) and submitted to sleep studies were evaluated. FeNO levels were measured following PSG.

Results: The average apnea hypopnea index (AHI) of patients was 37.8 ± 5.8 /hour, arousal index 56.7 ± 14.5 /hour, apnea index 19.0 ± 9.4 /hour and nadir oxygen saturation was 87 ± 4 %. The average level of FeNO was 27.7 ± 2.2 ppb. FeNO levels were positively correlated with AHI (R^2 = 0.3585, $p < 0.001$), arousal index (R^2 = 0.2598, $p < 0.001$), and apnea index (R^2 = 0.1719, $p < 0.01$).

Conclusion: This study demonstrates that airway inflammation was associated with OSA severity indices. Further study should be conducted in mild to severe OSA

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หยุดหายใจขณะนอนหลับดังนี้ ดัชนีการหยุดหายใจและหายใจแผ่ว (R^2 = 0.3585, p < 0.001) ดัชนีการตื่นเร้า (R^2 = 0.2598, p < 0.001) และดัชนีการหยุดหายใจ (R^2 = 0.1719, p < 0.01)

สรุป: การศึกษาครั้งนี้แสดงถึงความสัมพันธ์ระหว่างการอักเสบของทางเดินหายใจและระดับความรุนแรงของภาวะหยุดหายใจขณะนอนหลับจากการอุดกั้น การศึกษาครั้งต่อไปควรศึกษาในกลุ่มผู้ป่วยที่มีความรุนแรงของภาวะหยุดหายใจขณะนอนหลับ ที่มีความรุนแรงระดับเล็กน้อยถึงรุนแรงเพื่อให้ได้ความสัมพันธ์ดังกล่าวที่ชัดเจนยิ่งขึ้น

คำสำคัญ: ภาวะหยุดหายใจขณะนอนหลับจากการอุดกั้น, การอักเสบของทางเดินหายใจ

patients in order to definitely establish the association between airway inflammation and sleep apnea indices.

Keywords: Obstructive sleep apnea, Airway inflammation

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Introduction

Obstructive sleep apnea (OSA) is characterized by temporary blockage of the upper airway during sleep. These key events seem to be the consequence of the local, repeated mechanical trauma related to the intermittent hypoxia (IH)[1]. A potential mechanism involved is IH, which may induce the production of oxygen free radicals through the phenomenon of ischemia-reperfusion injury, and thereby cause local and systemic inflammation[2]. NO synthase (iNOS) is expressed in epithelial cells in response to pro-inflammatory cytokines and oxidants, probably mediated by activation of the transcription factor nuclear factor kappa B[3]. There is increased expression of iNOS in the epithelium of OSA patients[4].

Airway inflammation is closely linked to systemic inflammation and is known to play a fundamental role in the pathogenesis of endothelial dysfunction[5]. An American Thoracic Society (ATS) in 2011[6] provides guidelines for the use of fractional exhaled nitric oxide (FeNO) levels in a clinical practice. An elevated FeNO level is also a marker of eosinophilic airway inflammation, and can be used in the diagnosis and treatment evaluation of airway inflammation[5]. OSA patients showed higher FeNO levels compared to age- and weight-matched controls without OSA[5, 7]. Studies on the association between sleep apnea severity and airway inflammation showed either positive correlation[8, 9, 10] or no correlation[11]. We therefore investigated whether FeNO was associated with sleep apnea severity in Thai OSA patients.

Materials and Methods

Study design and population

This observational, non-randomized, and open-label study was approved by the Human Research Ethics Committee, KhonKaen University, and informed consent was obtained from each participant. Forty OSA patients aged between 30 to 70 years old volunteered to participate in the study were analyzed. All patients were recruited from the Sleep Disorder Clinics, the Faculty of Medicine (Srinagarind Hospital, KhonKaen University). All patients were diagnosed with medical specialists by the polysomnography (PSG). Clinically, patients with an apnea–hypopnea index (AHI) more than30 per hour with no history of cardiovascular disease were studied. Patients with history of central sleep apnea, autoimmune conditions, or symptoms of respiratory tract infection six weeks prior to the study were excluded.

Polysomnography

All patients underwent full-night PSG using a digital system at the Sleep Disorder Clinic at the Faculty of Medicine (Srinagarind Hospital, KhonKaen University). PSG was performed using a procedure described previously[7]. Apnea was defined as a decrease in amplitude of airflow of at least 90% for at least 10 seconds and continued respiratory effort. Similarly, hypopnea was defined as a reduction in airflow of at least 30% that coincided with a decrease in oxygen desaturation of at least 3% and/or the event associated with an arousal[10].

Fractional exhaled NO (FeNO)

FeNO levels were measured with the Quark NO breath (COSMED Srl, ITALY) with a single breath online method at constant flow of 50 ml/s or 12 seconds of exhalation of adults according to American Thoracic Society/European Respiratory Society guidelines, with a sensitivity of one part per billion (ppb)[6]. All subjects were asked to refrain from eating, drinking, and strenuous exercise for two hours prior to FeNO measurement.

Statistical analysis

Data are expressed as mean ± (S.D) and R^2. The relationships between variables were determined by linear regression. Statistical analyses were conducted using STATA version 13.0 (Stata Corp., College Station, TX). A p-value of less than 0.05 was considered statistically significant.

Results

The demographic characteristics of OSA patients are summarized in Table 1. Fifteen OSA patients were males and 25 were females. All OSA patients in this study were obese. Mean Epworth Sleepiness Scale score of 16 indicates the possibility of severe sleep apnea. Systolic blood pressure, diastolic blood pressure, and mean arterial pressure of all OSA patients were within normal ranges.

Table 1 Demographic characteristics of OSA patients

Parameters	OSA patients (n=40)
Age, years	47.0 (11.1)
Males/Females	15/25
Height, cm	164 (7.2)
Weight, kg	69.0 (10.9)
BMI, kg/m^2	25.8 (3.6)
Neck circumference, cm	34.0 (3.8)
Waist circumference, cm	85.0 (9.4)
Hip circumference, cm	95.0 (7.2)
Epworth sleepiness scale	16 (1.7)
Systolic blood pressure, mm Hg	126.4 (11.2)
Diastolic blood pressure, mm Hg	87.3 (12.8)
Mean arterial pressure, mm Hg	100.4 (10.8)

Data are expressed as mean (SD).

Polysomnographic data measured in OSA patients are shown in Table 2. AHI, respiratory effort related arousals (RERA), respiratory disturbance index (RDI), arousal index, apnea index, and lowest SpO_2 signify severe OSA. Sleep architecture parameters were within normal ranges. The average of FeNO levels was 27.7 ± 2.2 ppb which is indicative of airway inflammation.

Table 2 Sleep parameters and fractional exhaled nitric oxide

Parameters	OSA patients (n=40)
Polysomnography data	
Apnea hypopnea index, /h	37.8 (5.8)
Respiratory effort related arousals, /h	44.8 (13.4)
Respiratory disturbance index, /h	66.8 (13.9)
Arousal index, /h	56.7 (14.5)
Apnea index, /h	19 (9.4)
Hypopnea index, /h	18.8 (5.9)
Longest apnea or hypopneatime, sec	26 (14.9)
Lowest SpO_2, %	84.3 (4.3)
Sleep architecture data	
Total sleep time, min	347.7 (48.2)
Total time in bed, min	389.5 (40.2)
Sleep efficiency, %	87.5 (6.4)
Non rapid eye movement stage 1, %	28.7 (8.3)
Non rapid eye movement stage 2, %	29.4 (8.1)
Non rapid eye movement stage 3-4, %	17.9 (5.8)
Rapid eye movement, %	10.3 (5.8)
Wake, %	13.9 (4.3)
Fractional exhaled nitric oxide	
FeNO, ppb	27.7 (2.2)

Data are expressed as mean (SD).

The association between airway inflammation and sleep apnea severity is shown in Figures 1 to 3. The data show positive correlations between FeNO levels with severity of OSA (AHI) ($R^2 = 0.3585$, $p < 0.001$) (Figure 1), arousal index ($R^2 = 0.2598$, $p < 0.001$) (Figure 2), and apnea index during PSG ($R^2 = 0.1719$, $p < 0.01$) (Figure 3).

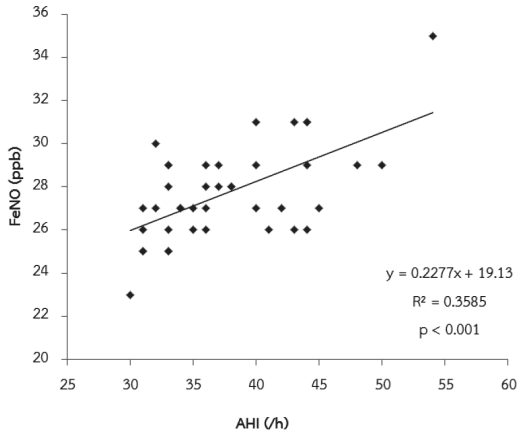

Figure 1 Correlation between FeNO levels and apnea hypopnea index

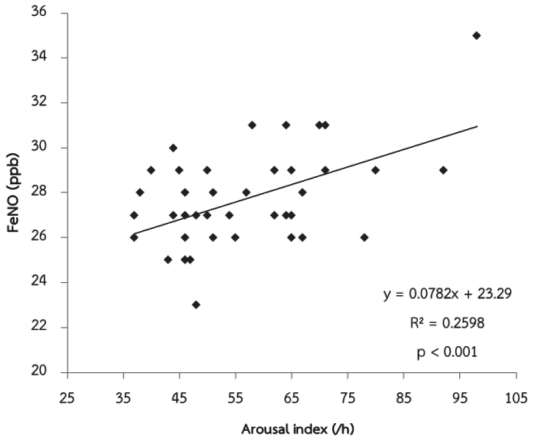

Figure 2 Correlation between FeNO levels and arousal index

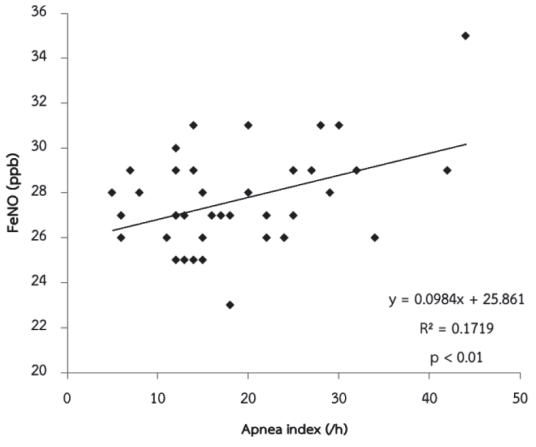

Figure 3 Correlation between FeNO levels and apnea index

Discussion

The main finding of this study was that FeNO levels are positively correlated with sleep apnea severity indices in severe OSA patients.

In the present study, we found that FeNO levels were positively correlated to sleep apnea severity indices including AHI, arousal index, and apnea index. This observation is consistent with previous studies that showed the association between FeNO with PSG parameters[8-10]. There has been only study failing to find the association of sleep severity with airway inflammation[11]. This discrepancy is due to differences in the severity of OSA patients included in each study. The latter study was done in mild OSA patients only, while the present study and other studies were conducted in severe or moderate to severe OSA patients.

NO is synthesized by the human lungs and is present in exhaled breath. NO has been implicated in the pathophysiology of airway inflammation[6], which in turn plays a key role in the pathogenesis of OSA. Airway inflammation in OSA patients may be a consequence of physical injury of the mucosal lining caused by IH, resulting in ischemia and reperfusion[13]. The positive correlation between FeNO levels and indices of sleep apnea severity observed in OSA patients indicates that as the severity of sleep apnea increases, there is a concomitant increase in IH-induced iNOS in endothelial cells and in NO production in airways[4]. This correlation may also reflect a systemic inflammatory response to hypoxemia, which is known to trigger activation of eosinophils. These eosinophils in turn interact with the endothelium of airways to cause an increase in NO via iNOS in patients with severe OSA[3, 14]. Moreover, it is likely that OSA patients with higher arousal index had a higher degree of hypoxemia, which triggered sympathetic overactivity[15], and ultimately caused airway inflammation and increased FeNO levels[2, 16].

Conclusion

In summary, this study found that airway inflammation was positively correlated with sleep apnea severity in severe OSA patients. Further study should be

conducted in mild to severe OSA patients to definitely establish the association between airway inflammation and sleep apnea indices.

Acknowledgments

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