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Apnea-hypopnea index prediction through an assessment of autonomic influence on heart rate in wakefulness

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HIGHLIGHTS

- New predictors of apnea-hypopnea index (AHI) were suggested.
- Cardiac response to deep inspiration breath hold affects the predictors.
- Reliable and time-efficient prediction of AHI was achieved by the predictors.

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ABSTRACT

With the high prevalence of obstructive sleep apnea, the issue of developing a practical tool for obstructive sleep apnea screening has been raised. Conventional obstructive sleep apnea screening tools are limited in their ability to help clinicians make rational decisions due to their inability to predict the apnea-hypopnea index. Our study aimed to develop a new prediction model that can provide a reliable apnea-hypopnea index value during wakefulness. We hypothesized that patients with more severe obstructive sleep apnea would exhibit more attenuated waking vagal tone, which may result in lower effectiveness in decreasing heart rate as a response to deep inspiration breath-holding. Prior to conducting nocturnal in-laboratory polysomnography, 30 non-obstructive sleep apnea (apnea-hypopnea index < 5 events/h) subjects and 246 patients with obstructive sleep apnea participated in a 75-second experiment that consisted of a 60-second baseline measurement and consecutive 15-second deep inspiration breath-hold sessions. Two apnea-hypopnea index predictors were devised by considering the vagal activities reflected in the electrocardiographic recordings acquired during the experiment. Using the predictors obtained from 184 individuals, regression analyses and *k*-fold cross-validation tests were performed to develop an apnea-hypopnea index prediction model. For the remaining 92 individuals, the developed model provided an absolute error (mean ± SD) of 3.53 ± 2.67 events/h and a Pearson's correlation coefficient of 0.99 ($P < 0.01$) between the apnea-hypopnea index predictive values and the reference values reported by polysomnography. Our study is the first to achieve reliable and time-efficient prediction of the apnea-hypopnea index during wakefulness.

1. Introduction

Obstructive sleep apnea (OSA), the most prevalent type of sleep-related breathing disorder (SRBD), is characterized by repetitive episodes of complete or partial upper airway obstruction, notwithstanding the effort to inhale [1]. With increasing number of obesity and elderly population, OSA has been considered a serious clinical concern. OSA is an independent cause of excessive daytime somnolence, tiredness, irritability, neurocognitive deficits, and depression [2]. Furthermore, undiagnosed and untreated OSA is a risk factor for critical complications such as cardiovascular and neurovascular diseases, metabolic disorders, and altered immune function [3,4]. A higher risk of postoperative cardiac events, respiratory failure, and intensive care unit (ICU) admission is associated with undiagnosed and untreated OSA [5].

Prior to conducting overnight in-laboratory polysomnography (PSG) or cardiorespiratory polygraphy, formal diagnostic tests for OSA, employing screening tools is useful for cost- and time-effective identification of patients with OSA. Most widely used screening tools for OSA are based on clinical predictors, including demographic (e.g., age and

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gender) and anthropometric (e.g., body mass index (BMI) and neck circumference) variables, observed apnea and hypopnea, and comorbid conditions (e.g., snoring, hypertension, and daytime symptoms, such as tiredness, fatigue, and excessive daytime sleepiness) [1,6–23]. Information regarding these variables is generally investigated through questionnaires and/or interviews. A different type of predictor, based on the anatomical and functional characteristics of the OSA patient's upper airway regarding acoustic speech signals, breathing sounds, and airway pressure signals acquired during wakefulness, is also used for OSA screening [24–30]. However, all existing predictors of OSA have a limitation in that they provide only dichotomously classified conjecture without respect to multiple categories of OSA severity, determined by an apnea-hypopnea index (AHI) value.

The aim of our study was to develop a new prediction model that can provide a reliable AHI value during wakefulness, which would be helpful in making more reasonable clinical decisions on the need and urgency of formal diagnoses and active therapeutic interventions for OSA. We hypothesized that patients with more severe OSA, expressed as higher AHI values and associated with more severe autonomic dysfunction, would exhibit greater attenuation of waking vagal tone, resulting in lower effectiveness in decreasing heart rate (HR) as a response to deep inspiration breath-holding (DIBH).

2. Materials and methods

2.1. Subjects and polysomnography

The Institutional Review Board of Seoul National University Hospital approved the study protocol (IRB No. 1603-127-750). Our study was performed with a total of 276 subjects who had been referred for diagnostic overnight PSG because of suspected OSA at the Center for Sleep and Chronobiology of Seoul National University Hospital. The suspected OSA patients were identified by a sleep physician in accordance with the Berlin questionnaire. The physiological parameters acquired during PSG (NEUVO, Compumedics Ltd., Victoria, Australia) were as follows: electroencephalogram (EEG) at F4-M1, C4-M1, and O2-M1 positions; bilateral electrooculogram (EOG); electromyogram (EMG) at the chin and anterior tibialis muscles; electrocardiogram (ECG) at lead II; body posture using a tri-axis accelerometer; nasal pressure using a nasal cannula/pressure transducer (PTAF2, Pro-Tech Services Inc., Mukilteo, Washington, USA); oronasal airflow using a thermocouple (Compumedics Ltd., Victoria, Australia); thoracic and abdominal volume changes using piezoelectric-type belts (zRIP DuraBelt, Pro-Tech Services Inc., Mukilteo, Washington, USA); blood oxygen saturation using a pulse oximeter (MARS, type 2001, Respironics Novametrix Inc., Murrysville, Pennsylvania, USA); and snoring sound using a microphone. All data were sampled at 250 Hz. Each polysomnographic recording was scored by certified sleep technologists and verified by sleep physicians in accordance with the 2012 American Academy of Sleep Medicine (AASM) manual. A respiratory event that met both of the following criteria was scored as an apnea: there is a drop in the peak signal excursion by ≥90% of pre-event baseline using an oronasal thermal sensor; and the duration of the ≥90% drop in sensor signal is ≥10 s [31]. A hypopnea was determined when a respiratory event met all of the following criteria: the peak signal excursions drop by ≥30% of pre-event baseline using nasal pressure; the duration of the ≥30% drop in signal excursion is ≥10 s; and there is a ≥3% oxygen desaturation from pre-events baseline or the event is associated with an arousal [31]. The number of apneas and hypopneas per hour of sleep were defined as the apnea index (AI) and hypopnea index (HI), respectively. The sum of the AI and HI was designated as AHI_{Refer}, denoting the AHI reference value.

According to the AHI_{Refer} value, subjects were classified as non-OSA ($AHI_{Refer} < 5$ events/h) subjects, and mild OSA ($5 \le AHI_{Refer} < 15$ events/h), moderate OSA ($15 \le AHI_{Refer} < 30$ events/h), and severe OSA ($AHI_{Refer} \ge 30$ events/h) patients. The four gender ratio- and age-matched groups consisted of 30 (non-OSA), 60 (mild OSA), 90 (moderate OSA), and 96 (severe OSA) individuals. The exclusion criteria for all groups were 1) the presence of cardiovascular disease (e.g., hypertension, myocardial ischemia, myocardial infarction, and heart failure), 2) the presence of other psychiatric or medical conditions known to be associated with the autonomic nervous system (ANS) (e.g., pure autonomic failure), and 3) the use of medications known to influence ANS function. Hypertension was defined as the current use of antihypertensive drugs or a systolic blood pressure (BP) ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg. The demographic and anthropometric characteristics and sleep-related parameters of the study subjects are summarized in Table 1.

2.2. Experimental procedure

From 5 to 30 min prior to carrying out PSG, each subject performed an experiment that consisted of two consecutive sessions. The first session was a baseline measurement session. With the subject in the supine position, spontaneous and habitual breathing was required for 60 s during the baseline measurement session. Immediately thereafter, the second session, the breath-hold session, was initiated and the subject was instructed to perform DIBH for 15 s while remaining in the supine position. All subjects were required to avoid taking exercise, nicotine, alcohol, and caffeinated foods and beverages for an hour prior to the experiment.

During the experiment, nasal pressure was measured using a nasal cannula/pressure transducer (PTAF2, Pro-Tech Services Inc., Mukilteo, Washington, USA), and a single-lead ECG (lead II) was recorded. The nasal pressure signals were observed to confirm the accomplishment of DIBH.

Table 1
Demographic and anthropometric characteristics and sleep-related parameters of study subjects.

	Non-OSA	Mild OSA	Moderate OSA	Severe OSA
Sample size (male/female)	30 (23/7)	60 (45/15)	90 (68/22)	96 (72/24)
Age (years)	46.8 ± 14.0	47.6 ± 15.1	48.4 ± 13.4	48.5 ± 12.8
BMI (kg/m^2)	23.5 ± 2.7	24.3 ± 2.3	26.3 ± 4.0*,†	27.8 ± 3.2*,†
ESS score	7.1 ± 2.7	7.8 ± 2.6	8.0 ± 2.8	9.6 ± 3.0*,†,‡
TRT (min)	502.6 ± 34.3	489.7 ± 32.0	500.8 ± 31.5	490.0 ± 33.5
SE (%)	89.0 ± 8.1	88.6 ± 7.5	86.1 ± 9.8	86.0 ± 8.3
AHI_{Refer} (events/h)	2.5 ± 1.6	9.7 ± 2.8*	22.5 ± 4.3*,†	64.0 ± 21.2*,†,‡

OSA, obstructive sleep apnea; BMI, body mass index; ESS, Epworth Sleepiness Scale; TRT, total recording time; SE, sleep efficiency; AHI_{Refer}, apnea-hypopnea index reported by polysomnography.
Subjects were classified according to their AHI_{Refer} value into non-OSA ($AHI_{Refer} < 5$ events/h), mild OSA ($5 \le AHI_{Refer} < 15$ events/h), moderate OSA ($15 \le AHI_{Refer} < 30$ events/h), and severe OSA ($AHI_{Refer} \ge 30$ events/h) groups.
Data are presented as the mean ± SD.
* $P < 0.05$ in comparison to the non-OSA group;
† $P < 0.05$ in comparison to the mild OSA group;
‡ $P < 0.05$ in comparison to the moderate OSA group (independent samples *t*-test).