공학박사 학위논문

# Prediction of Sleep Efficiency and Apnea-Hypopnea Index with Cardiorespiratory Signals Obtained During Sleep-Onset Period

입면 구간의 심폐신호를 이용한

수면 효율과 무호흡-저호흡 지수의 예측

2017년 2월

서울대학교 대학원

협동과정 바이오엔지니어링 전공

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이 논문을 공학박사 학위논문으로 제출함
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**Ph.D. Dissertation**

# Prediction of Sleep Efficiency and Apnea-Hypopnea Index with Cardiorespiratory Signals Obtained During Sleep-Onset Period

**February 2017**

**Interdisciplinary Program of Bioengineering**
**Seoul National University**
**Graduate School**

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**Submitting the Ph.D. Dissertation**

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# Abstract

## Prediction of Sleep Efficiency and Apnea-Hypopnea Index with Cardiorespiratory Signals Obtained During Sleep-Onset Period

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Interdisciplinary Program of Bioengineering

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This study aimed to propose new effective predictors of sleep parameters using cardiorespiratory signals obtained during the sleep-onset period.

First, I attempted to predict sleep efficiency. Sleep efficiency is defined as the ratio between actual sleep time and time spent in bed and the most commonly used measure for the objective assessment of sleep quality. Monitoring sleep efficiency can provide significant information regarding health conditions. It was possible to hypothesize that the autonomic nervous system activity observed before sleep may be associated with sleep efficiency. To assess autonomic activity in the awake resting state, heart rate variability

and breathing parameters were analyzed for 5 min. Using these parameters, stepwise multiple linear regression analyses and *k*-fold cross-validation tests were performed for 240 electrocardiographic and thoracic volume change signal recordings to develop a sleep efficiency prediction model. The model's sleep efficiency predictability was evaluated using 60 piezoelectric sensor signal recordings. A regression model was constructed using the power ratio of the low- and high-frequency bands of the heart rate variability signal and the average peak inspiratory flow rate. This model exhibited an absolute error (mean ± SD) of 2.18 ± 1.61% and a Pearson's correlation coefficient of 0.94 ($P < 0.01$) between the sleep efficiency predictive values and reference values measured with polysomnography. The prediction model has the potential to be utilized for home-based, long-term monitoring of sleep efficiency, and to support effective decision-making regarding the application of sleep efficiency improvement strategies.

Second, I attempted to predict the apnea-hypopnea index in obstructive sleep apnea patients. The apnea-hypopnea index is defined as the number of apnea and hypopnea events per hour of sleep and the most widely used quantitative measure for the determination of obstructive sleep apnea severity. With the high prevalence of obstructive sleep apnea, the issue of developing a practical tool for obstructive sleep apnea screening has been raised. Because conventional obstructive sleep apnea screening tools cannot predict the apnea-hypopnea index, their applicability is limited. Here, three predictors of

the apnea-hypopnea index were suggested based on the following hypotheses: 1) during the sleep-wake transition period, less irregular respiration cycles would be observed in patients with more severe obstructive sleep apnea, and 2) patients with more severe obstructive sleep apnea would exhibit more attenuated waking vagal tone, which might produce lower effectiveness in decreasing heart rate as a response to deep inspiration breath-holding. Using the three predictors extracted from 120 electrocardiographic recordings, nonlinear regression analyses and *k*-fold cross-validation tests were performed to develop an apnea-hypopnea index prediction model. For 30 piezoelectric sensor signal recordings, the model exhibited an absolute error (mean ± SD) of 2.66 ± 1.97 events/h and a Pearson's correlation coefficient of 0.99 ($P < 0.01$) between the apnea-hypopnea index predictive values and reference values measured with polysomnography. The developed apnea-hypopnea index prediction model could be potentially useful to make more reasonable clinical decisions on the need for formal diagnosis and treatment of obstructive sleep apnea.

**Keywords:** Sleep efficiency, apnea-hypopnea index, obstructive sleep apnea, sleep-onset period, cardiorespiratory signal, piezoelectric sensor

**Student Number:** 2011-21131

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# List of Abbreviations

| | |
|---|---|
| **AASM** | American Academy of Sleep Medicine |
| **AHI** | apnea-hypopnea index |
| **ANS** | autonomic nervous system |
| **BCG** | ballistocardiogram |
| **BMI** | body mass index |
| **BP** | blood pressure |
| **CCR** | correct classification rate |
| **CDR** | correct detection rate |
| **CV** | coefficient of variation |
| **DIBH** | deep inspiration breath-holding |
| **ECG** | electrocardiogram |
| **EDR** | electrocardiogram-derived respiration |
| **HF** | high-frequency band (0.15–0.4 Hz) of heart rate variability |
| **HR** | heart rate |
| **HRQoL** | health-related quality of life |
| **HRR-1** | heart rate recovery during the first minute after exercise |
| **HRV** | heart rate variability |
| **LF** | low-frequency band (0.04–0.15 Hz) of heart rate variability |
| **MAE** | mean absolute error |

| | |
|---|---|
| **NN** | normal-to-normal sinus |
| **NPV** | negative predictive value |
| **OSA** | obstructive sleep apnea |
| **OSAS** | obstructive sleep apnea syndrome |
| **Pd** | P-wave dispersion |
| **PIFR** | peak inspiratory flow rate |
| **PLMS** | periodic limb movements in sleep |
| **PLMSI** | periodic limb movements in sleep index |
| **PPV** | positive predictive value |
| **PSG** | polysomnography |
| **PVDF** | polyvinylidene fluoride |
| **QTc** | QT-corrected interval |
| **RMSSD** | square root of the mean squared difference between successive normal-to-normal sinus intervals |
| **ROC-AUC** | area under the receiver operating characteristics curve |
| **SCI** | spinal cord injury |
| **SE** | sleep efficiency |
| **SL** | sleep latency |
| **SRBD** | sleep-related breathing disorder |
| **TRT** | total recording time |
| **TST** | total sleep time |
| **WASO** | wake after sleep onset |

# Chapter 1. Introduction

## 1.1. Background

### 1.1.1. Sleep parameter

Human beings spend approximately one-third of their lives asleep. During sleep, the body and the nervous system can recuperate and the formation and synthesis of protein are activated [1]. Because sleep significantly affects individuals' quality of life and health, the importance of sleep management has been emphasized [2, 3]. The objective assessment of sleep is an essential first step in managing sleep health. This assessment involves the use of sleep parameters, which include quantitative measures related to sleep structure and arousal, movement, cardiac, and respiratory events that occur during sleep [4]. This dissertation focuses on two key sleep parameters: sleep efficiency (SE), which is the most important sleep structure parameter, and the apnea-hypopnea index (AHI), which is the principal respiratory event parameter.

#### 1.1.1.1. Sleep efficiency

SE, which is defined as the ratio between actual sleep time and time spent in bed, is the most commonly used quantitative measure for the objective assessment of sleep quality [4]. Åkerstedt *et al*. investigated the meaning of "good sleep" and concluded that it is more closely related to SE than to sleep continuity variables, such as sleep latency (SL; the time required to reach the

first epoch (30-s segment) scored as any sleep stage other than wakefulness after lights out), final wake time, and wake after sleep onset (WASO) [5]. Hasler *et al.* demonstrated that a higher SE indicates more consolidated sleep because the calculation of SE involves all sleep continuity variables [6].

SE monitoring is an important issue that has drawn considerable attention in medicine and healthcare because many studies have demonstrated that a low SE is a significant feature of poor health and pathological conditions. Hoffstein *et al*. reported that SE was significantly negatively correlated with the snoring index [7]. Janson *et al*. determined that asthmatic subjects had a low SE [8]. Iliescu *et al*. observed a significant positive association between physical health-related quality of life (HRQoL) and SE in hemodialysis patients [9]. Aydoğdu *et al*. demonstrated that patients with interstitial lung disease had a poor SE [10]. Blackwell *et al.* reported that a lower SE was associated with a higher risk of cognitive impairment in older women, whereas total sleep time (TST) was not [11]. Scheer *et al*. observed that patients with cervical spinal cord injury (SCI) had a significantly lower SE than thoracic SCI patients and healthy control subjects [12]. Gruber *et al*. demonstrated that the effectiveness of methylphenidate and its impact on tasks, which require vigilance and sustained attention, were associated with SE in children with attention deficit hyperactivity disorder [13]. Yu *et al.* observed a low SE in patients with mild cognitive impairment and Alzheimer's disease [14]. Wong *et al*. reported that habitual SE was a

significant predictor of academic functioning, physical well-being, and psychological health [15].

#### 1.1.1.2. Apnea-hypopnea index in obstructive sleep apnea

Obstructive sleep apnea (OSA) is the most prevalent type of sleep-related breathing disorder (SRBD). OSA is characterized by the recurrence of complete or partial upper airway obstruction during sleep, intermittently causing cessations of breathing (apneas) or reductions of airflow (hypopneas) notwithstanding the effort to inhale [16]. With the increase in obesity and the ageing population, OSA has been considered a serious clinical concern. OSA is an independent contributor to excessive daytime somnolence, neurocognitive deficits, tiredness, irritability, and depression [17]. Furthermore, undiagnosed and untreated OSA is a risk factor for life-threatening complications, such as cardiovascular and neurovascular diseases, metabolic disorders, and altered immune function [18]. Among postoperative patients, more frequent cardiorespiratory complications have been reported for unattended OSA cases compared to patients treated for OSA prior to surgery [19].

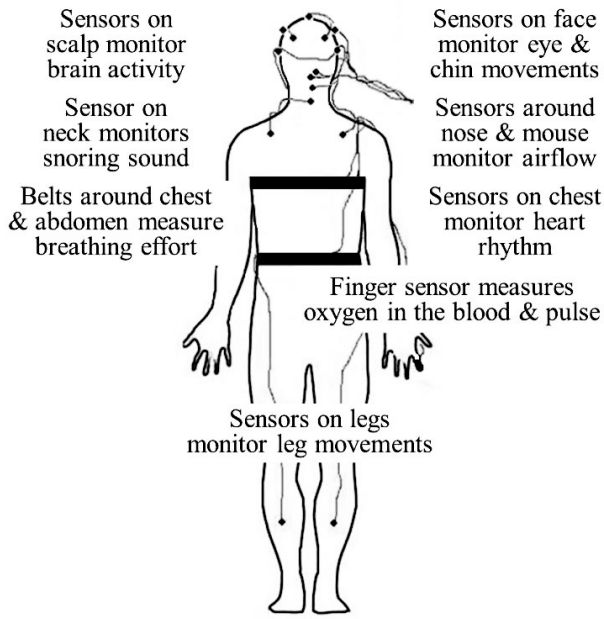
The AHI, defined as the number of apnea and hypopnea events per hour of sleep, is the most commonly used quantitative measure to determine OSA severity. Previous studies have demonstrated that a higher AHI in OSA patients was associated with a higher risk of comorbidities. Ciftci *et al*.

reported that inflammatory cytokines, such as interleukin-6 and tumor necrosis factor-alpha levels, were significantly correlated with the AHI in OSA patients [20]. Bassetti *et al*. observed that diabetes, hypertension, coronary heart disease, and the macroangiopathic etiology of stroke were significantly prevalent in OSA patients with AHI ≥ 30 events/h compared to OSA patients with AHI < 10 events/h [21].

### 1.1.2. Sleep parameter prediction

Overnight in-laboratory polysomnography (PSG) is the gold standard method to obtain sleep parameters, including the SE and AHI. Figure 1-1(a) shows the sensors used in standard PSG, and Figure 1-1(b) displays typical physiological data monitored and recorded during standard PSG. Sleep technologists analyze physiological data recorded during PSG and score the sleep stage and sleep-associated events to provide information on the sleep parameters. Predicting sleep parameters without overnight recording can be useful in terms of time and resource efficiency and the potential to improve sleep, which cannot be achieved by evaluating sleep parameters through whole-night monitoring.

(a)




(b)

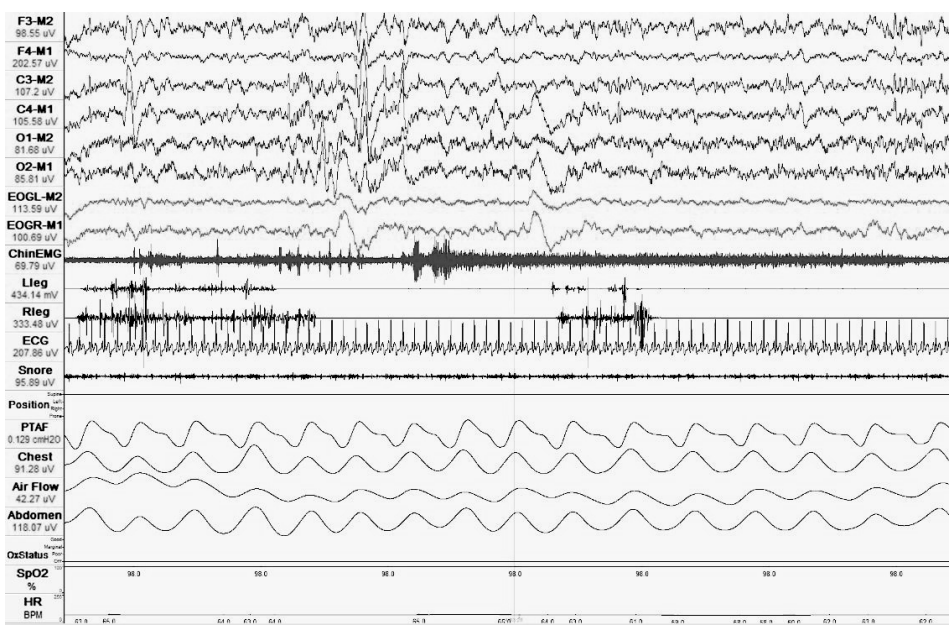



**Figure 1-1.** (a) Sensors used in standard polysomnography (PSG). (b) Physiological data monitored and recorded during standard PSG.

Specifically, SE prediction could provide information that is helpful to establish effective strategies for improving SE. The use of predictive SE values could enable effective decision-making regarding the strictness and intensity of SE improvement strategies, such as biofeedback training, prior to their implementation.

The prediction of the AHI would be useful to make more reasonable clinical decisions on the necessity and urgency of formal diagnoses and active therapeutic interventions for OSA. AHI prediction could also help anesthesiologists and surgeons to reduce postoperative complications related to OSA [19, 22, 23].

## 1.2. Problem statement

### 1.2.1. Sleep efficiency prediction

Previous studies have reported meaningful associations between SE and demographic characteristics (e.g., sex [24] and age [25]), daily energy expenditure [26], diet (e.g., caffeine [27] and alcohol [28] consumption), psychosocial factors (e.g., loneliness and social ties [29]), and environmental characteristics (e.g., noise [30], lighting [31], temperature, and humidity [32]). Although many SE factors have been identified, their utilization in predicting SE has been limited, possibly because of their insufficient predictive ability.

### 1.2.2. Obstructive sleep apnea prediction

Most widely used screening tools for OSA are based on clinical predictors, including demographic (e.g., age and 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) [16, 22, 23, 33-48]. Information on these variables is generally obtained through questionnaires and/or interviews. Additionally, OSA screening can utilize a different type of predictor, which is based on the anatomical and functional characteristics of an OSA patient's upper airway; these involve acoustic speech signals, breathing sounds, and airway pressure signals acquired during waking [49-55]. However, all existing OSA predictors have limitations, as they provide only binary classification without considering multiple categories of OSA severity, which are determined by the AHI value.

## 1.3. Purpose

This study aimed to determine new reliable SE and AHI predictors. Because cardiorespiratory features are known to be effective indicators of neurophysiological states and can be obtained with minimal discomfort to the subject, I analyzed cardiorespiratory signals obtained during the sleep-onset period and extracted the predictors from them.

## 1.4. Dissertation outline

This dissertation consists of the following chapters.

- Chapter 2 describes the physiological approach and methodological strategy for the development and evaluation of an SE prediction model and discusses the potential applicability of the model.
- Chapter 3 outlines the physiological approach and methodological strategy for the development and evaluation of AHI prediction models and examines the potential applicability of the models.
- Chapter 4 presents the overall discussion.
- Chapter 5 summarizes the conclusions of the preceding chapters.

This dissertation is based on the following publications.

- Chapter 2

  D. W. Jung, Y, J. Lee, D. -U. Jeong, and K. S. Park, "New predictors of sleep efficiency," *Chronobiology International*.

- Chapter 3

  D. W. Jung, S. H. Hwang, Y. J. Lee, D. -U. Jeong, and K. S. Park, "Apnea-hypopnea index prediction using electrocardiogram acquired during sleep-onset period," *IEEE Transactions on Biomedical Engineering*.

  D. W. Jung, Y. J. Lee, D. -U. Jeong, and K. S. Park, "Apnea-hypopnea index prediction through an assessment of autonomic influence on

heart rate in wakefulness," *Physiology & Behavior*.

The author of this dissertation contributed to the above studies as follows: conception and design of the experiments; data acquisition, analysis, and interpretation; and drafting and revising of the manuscript for important intellectual content.

# Chapter 2. Sleep Efficiency Prediction

## 2.1. Hypothesis

This study hypothesized that the physiological state observed before sleep could be associated with SE. Because of the close relationship between sleep and autonomic nervous system (ANS) activity, it was possible to hypothesize that greater sympathetic activation (parasympathetic inhibition) before sleep could be associated with lower SE. Based on existing studies that showed that heart rate variability (HRV) and breathing parameters have a significant relationship with ANS activity, these parameters were extracted and used to develop an SE prediction model [56, 57].

## 2.2. Methods

### 2.2.1. Datasets

The Institutional Review Board of Seoul National University Hospital approved this retrospective study and waived the patient consent requirement (IRB No. 1603-127-750). The subjects, who had complaints about their habitual sleep patterns regarding onset latency, duration, and quality, owing to various causes, were recruited through an announcement posted in the Seoul National University Hospital.

The exclusion criteria for the study subjects were as follows: 1) the presence of parasomnia (e.g., bruxism, sleep paralysis, sleep enuresis,

confusional arousal, sleepwalking, nightmares, night terrors, nocturnal sleep-related eating disorder, or rapid eye movement sleep behavior disorder); and 2) the presence of other psychiatric or medical conditions known to be associated with ANS activity (e.g., pure autonomic failure).

All subjects were required to avoid napping, excessive exercise, nicotine, alcohol, caffeinated foods and beverages, tranquilizers, and sleeping pills on the day of the PSG. The temperature and humidity of the sleep laboratory were controlled between 18°C and 25°C and between 45% and 55%, respectively, depending on the season and the requirements of each subject. The PSG initiation time was determined by subjects depending on their habitual sleep patterns.

Two gender ratio- and age-matched groups, the low- and high-SE groups, were organized from two datasets. The first dataset, designated as Dataset I, was constructed to verify the study hypothesis using HRV and breathing parameters obtained from reference cardiorespiratory signals. This dataset included 240 subjects who had undergone overnight PSG at the Center for Sleep and Chronobiology of Seoul National University Hospital between July 2012 and January 2013. Prior to sleep, an electrocardiogram (ECG; lead II) and thoracic volume change signals, measured using a piezoelectric-type belt (zRIP DuraBelt, Pro-Tech Services Inc., Mukilteo, Washington, USA), were acquired for 6 min from each subject who was in the awake resting supine position. The second dataset, designated as Dataset II, was organized to

evaluate the practical applicability of the study hypothesis using HRV and breathing parameters extracted from unobtrusively measured cardiorespiratory signals. This dataset consisted of 60 subjects who had undergone overnight PSG at the Center for Sleep and Chronobiology of Seoul National University Hospital between July 2012 and October 2013. Before sleep, an ECG and thoracic volume change signals were simultaneously acquired with piezoelectric sensor signals, measured using a polyvinylidene fluoride (PVDF) film sensor-based system, for 6 min from the subjects who were in the awake resting supine position. The 4 × 1 array of PVDF film sensors, which had an area of 300 mm × 300 mm × 0.1 mm (length × width × height), was placed between the mattress and its cover under the dorsal surface [58, 59]. Figure 2-1(a) and (b) show the PVDF film sensor array's placement and dimensions, respectively. The piezoelectric data were sampled at 250 Hz.

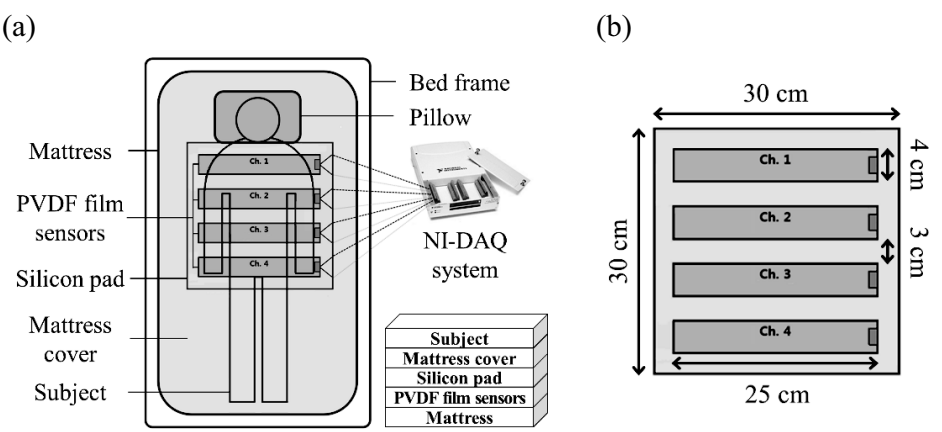



**Figure 2-1.** Polyvinylidene fluoride (PVDF) film sensor array: (a) placement on the bed mattress, and (b) dimensions.

During the physiological signal acquisition period, all subjects in both datasets were instructed not to drowse or fall asleep and their wakeful state was monitored and confirmed by certified sleep technologists.

The nocturnal PSG recordings were obtained using an NI-DAQ 6221 (National Instruments, Austin, Texas, USA) at a sampling rate of 250 Hz. The recordings were scored by certified sleep technologists and verified by sleep physicians in accordance with the 2012 American Academy of Sleep Medicine (AASM) manual [4]. From each polysomnographic recording, the TST (in minutes) and total recording time (TRT; "lights out" to "lights on" in minutes) were determined and used to calculate the SE ([TST/TRT] × 100). The subjects with SE < 85% were classified as the low-SE group, while those with SE ≥ 85% were classified as the high-SE group. The low- and high-SE groups contained 40 and 81 patients with sleep apnea (AHI ≥ 5 events/h), 12 and 20 patients with periodic limb movements in sleep (PLMS) (PLMS index (PLMSI) ≥ 15 events/h)), 37 and 65 patients with hypertension, 6 and 7 patients with diabetes, 1 and 2 patients with angina, 2 and 3 patients with arrhythmia, and 6 and 14 patients with hyperlipidemia, respectively.

The demographic and anthropometric characteristics and sleep parameters of the two datasets are summarized in Table 2-1.

**Table 2-1.** Demographic and anthropometric characteristics and sleep parameters of the subjects in Datasets I and II

| | Dataset I | | Dataset II | |
|---|---|---|---|---|
| | Low-SE group | High-SE group | Low-SE group | High-SE group |
| Number of subjects (male/female) | 74 (46/28) | 166 (103/63) | 19 (12/7) | 41 (26/15) |
| Age (years) | 43.0 ± 14.8 | 43.1 ± 15.9 | 43.1 ± 11.7 | 43.1 ± 10.9 |
| BMI (kg/m$^2$) | 24.3 ± 3.5 | 24.6 ± 3.3 | 24.5 ± 2.5 | 24.5 ± 3.7 |
| TRT (min) | 506.8 ± 37.9 | 509.1 ± 38.6 | 515.2 ± 40.3 | 514.0 ± 41.2 |
| TST (min) | 397.4 ± 38.5 | 468.0 ± 40.6* | 399.5 ± 36.0 | 473.0 ± 48.1† |
| SE (%) | 78.5 ± 6.2 | 91.9 ± 3.8* | 77.7 ± 6.9 | 92.1 ± 3.7† |
| WASO (min) | 95.5 ± 37.0 | 33.2 ± 19.2* | 97.6 ± 44.4 | 32.0 ± 19.3† |
| Stage N1 (%) | 21.9 ± 13.8 | 18.3 ± 10.2 | 20.9 ± 11.7 | 18.0 ± 10.9 |
| Stage N2 (%) | 51.5 ± 11.5 | 52.1 ± 11.1 | 52.1 ± 10.1 | 52.8 ± 11.3 |
| Stage N3 (%) | 7.5 ± 8.3 | 9.0 ± 9.2 | 7.6 ± 8.5 | 8.8 ± 9.0 |
| Stage R (%) | 19.1 ± 6.9 | 20.7 ± 6.7 | 19.4 ± 4.5 | 20.4 ± 6.6 |
| SL (min) | 13.9 ± 13.4 | 7.8 ± 8.3* | 18.1 ± 15.1 | 9.0 ± 11.2† |
| AHI (events/h) | 18.0 ± 20.8 | 15.5 ± 18.5 | 18.5 ± 18.6 | 15.3 ± 17.4 |
| PLMSI (events/h) | 4.6 ± 8.8 | 4.0 ± 9.3 | 4.7 ± 9.7 | 3.8 ± 7.5 |

SE, sleep efficiency; BMI, body mass index; TRT, total recording time; TST, total sleep time; WASO, wake after sleep onset; Stage N1, N2 and N3, percentage of time spent in non-rapid eye movement sleep stage 1, 2, and 3, respectively; Stage R, percentage of time spent in rapid eye movement sleep stage; SL, sleep latency; AHI, apnea-hypopnea index; PLMSI, periodic limb movements in sleep index.

Subjects were classified according to their SE values into the low-SE (SE < 85%) and high-SE (SE ≥ 85%) groups.

Data are presented as the mean ± SD.

*$P$ < 0.05 (independent samples $t$-test between the low- and high-SE groups); †$P$ < 0.05 (Mann-Whitney test between the low- and high-SE groups).

### 2.2.2. Data analysis

Band-pass (0.5–35 Hz) and low-pass (0.5 Hz) filters were applied to the ECG and thoracic volume change signals, respectively. Each of the piezoelectric sensor signals was band-pass (0.5–20 Hz) filtered to obtain a ballistocardiogram (BCG). Low-frequency fluctuations in the piezoelectric sensor signals, corresponding to respiratory effort signals, were acquired by low-pass (0.5 Hz) filtering.

#### 2.2.2.1. Parameter extraction

Because the first 1 min of the 6-min physiological signal acquisition period was considered as time for circumstantial adaptation, the following parameters were extracted from the physiological signals measured in the remaining 5 min.

*Heart rate variability parameters*

After R peaks on the filtered ECG and J peaks on the BCG were detected, normal-to-normal sinus (NN) intervals were obtained by removing the outliers from the RR and JJ intervals. Outliers caused by false or missed peak detections were identified by a sliding window filter with a length of 2,501 data points. Central points lying outside 20% of the window average were eliminated. From the NN intervals, three nonlinear HRV parameters, SD1, SD2 (standard deviations of the Poincaré plot), and SampEn (sample entropy),

were computed. The following HRV time-domain parameters were also extracted: SDNN (standard deviation of NN intervals), RMSSD (square root of the mean squared difference between successive NN intervals), NN50 (number of successive NN interval pairs that differ by more than 50 ms), and pNN50 (NN50 divided by the total number of NN intervals). The HRV frequency-domain analysis was conducted according to the following procedure. The NN interval time series were resampled at 4 Hz using cubic spline interpolation. The data in each of the three overlapping 512-sample subwindows of the 1,024-sample window were linearly detrended and windowed using a Hamming function. The spectral power over the 1,024-sample window was computed using a fast Fourier transform, and the following parameters were calculated: the peak frequency of the low-frequency (LF) band (0.04–0.15 Hz) and high-frequency (HF) band (0.15–0.4 Hz), absolute power of the LF and HF bands, power of the LF and HF bands in normalized units, and ratio between the LF and HF band powers (LF/HF). The very-low-frequency band (0.003–0.04 Hz) component was not extracted to avoid ambiguity in the data interpretation that could be caused by the analysis of insufficient amounts of data [60].

*Breathing parameters*

The following features were extracted from the filtered thoracic volume change signals and the respiratory effort signals, which were derived from the

piezoelectric sensor signals: breathing cycle (BC; in seconds), which denotes the time interval between two successive maximum peaks induced by inspirations; inspiratory time (IT; in seconds) and expiratory time (ET; in seconds), which indicate the time spent inhaling and exhaling during each breath, respectively; peak inspiratory flow rate (PIFR; in volts per second) and peak expiratory flow rate (PEFR; in volts per second), which correspond to the maximum inspiratory and expiratory flow rates during each breath, respectively; and inspiratory volume (IV; in volts) and expiratory volume (EV; in volts), which represent the volume changes (peak-to-peak value) in each breath caused by inspiration and expiration, respectively.

Finally, the average, standard deviation, and coefficient of variation (CV) of these features were computed and categorized as breathing parameters. In the following, each breathing parameter is designated with a subscript indicating each feature; for instance, $PIFR_{avg}$ denotes the average of PIFR values.

### 2.2.2.2. Statistical analysis

To validate the reliability of the piezoelectric sensor signals, correlation analysis was performed to the NN interval time series obtained from the ECG and BCG. The significance of the differences between the thoracic volume change signals and the respiratory effort signals was also tested.

Stepwise multiple linear regression analysis and *k*-fold cross-validation

testing were employed to develop an SE prediction model using the suggested parameters obtained from Dataset I. The regression model that provided the smallest *k*-fold cross-validation error was identified, and the corresponding predictors were analyzed in terms of their relationships with SE and clinical features. Changes in their values during sleep were also observed. The performance of the developed SE prediction model was evaluated using Dataset II.

All statistical analyses were performed using SPSS statistics software (v.21.0, SPSS Inc., Chicago, Illinois, USA).

## 2.3. Results

### 2.3.1. Piezoelectric sensor signal reliability validation

Figure 2-2 shows simultaneously recorded ECG, BCG, and thoracic volume change and respiratory effort signals. The Pearson's correlation coefficient (mean ± SD) between the ECG- and BCG-derived NN interval time series was 0.96 ± 0.01 (all $P < 0.01$). For all pairs of thoracic volume change and respiratory effort signals, significant differences were not observed (paired samples *t*-test, all $P > 0.05$).

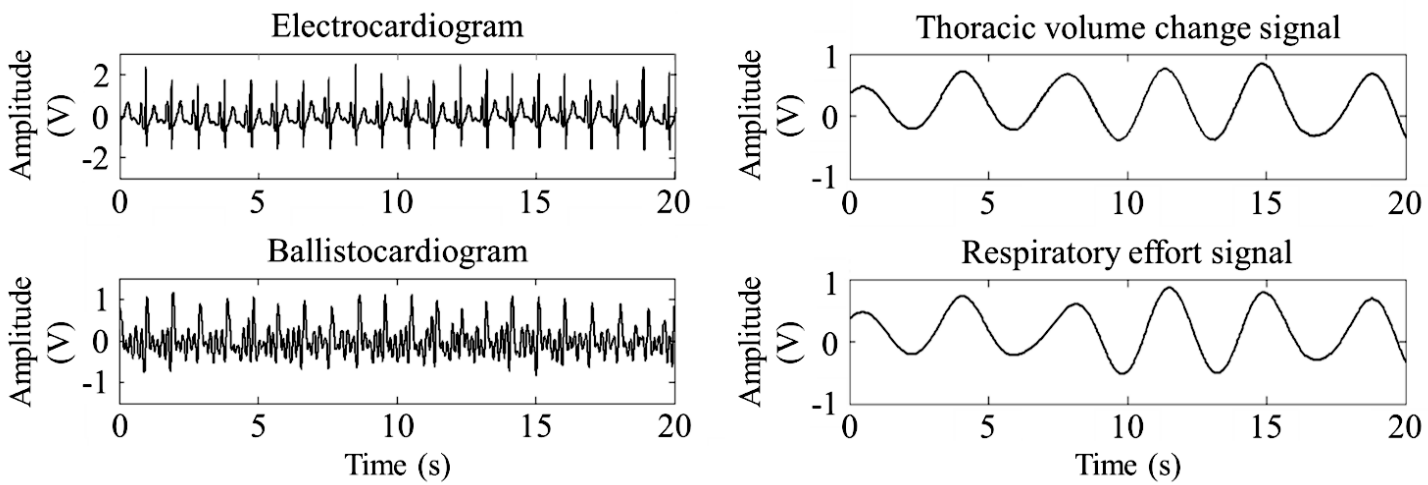



**Figure 2-2.** Simultaneously recorded electrocardiogram, ballistocardiogram (BCG), and thoracic volume change and respiratory effort signals. The BCG and respiratory effort signals were derived from the polyvinylidene fluoride film sensor signals.

### 2.3.2. Sleep efficiency prediction model development

The statistical results of the stepwise multiple linear regression analyses and 4-, 6-, 8-, and 10-fold cross-validation tests are summarized in Table 2-2. The statistics on mean absolute error (MAE) and Pearson's correlation coefficient in Table 2-2 were computed with $SE_{Predi}$, which denotes the SE predictive value, and $SE_{Refer}$, which indicates the SE reference value measured with PSG.

**Table 2-2.** Cross-validation statistics for sleep efficiency predictive models

| Cross-validation | MAE (%) | | Pearson's correlation coefficient | |
|---|---|---|---|---|
| | Training set | Validation set | Training set | Validation set |
| 4-fold | 2.26 ± 0.05 | 2.30 ± 0.17 | 0.93 ± 0.00 | 0.93 ± 0.01 |
| 6-fold | 2.26 ± 0.03 | 2.30 ± 0.14 | 0.93 ± 0.00 | 0.93 ± 0.01 |
| 8-fold | 2.26 ± 0.03 | 2.30 ± 0.25 | 0.93 ± 0.00 | 0.93 ± 0.01 |
| 10-fold | 2.27 ± 0.04 | 2.30 ± 0.40 | 0.93 ± 0.00 | 0.93 ± 0.02 |

MAE, mean absolute error.

The MAE values and Pearson's correlation coefficients were calculated between the sleep efficiency predictive values and reference values measured with polysomnography.

Data are presented as the mean ± SD.

$P < 0.01$ for all Pearson's correlation coefficients.

Figure 2-3 represents the regression model that provided the smallest *k*-fold cross-validation error ($k$ = 4, 6, 8, and 10). The best-fitting model (Figure 2-3, gray plane) to the training data (Figure 2-3, hollow circles) was developed using two predictors, LF/HF and $PIFR_{avg}$. Multicollinearity tests showed that the variance inflation factor values were less than 10 for all predictors. The representation of the regression function is summarized in Table 2-3, along with the adjusted coefficient of determination ($R^2$) value. For the training set including the data of 200 individuals with an $SE_{Refer}$ value (mean ± SD) of 87.8 ± 7.8%, an absolute error (mean ± SD) of 2.30 ± 1.87% and a Pearson's correlation coefficient of 0.93 ($P < 0.01$) were obtained between $SE_{Predi}$ and $SE_{Refer}$. For the validation set that consisted of the data of the remaining 40 individuals (Figure 2-3, filled triangles) with an $SE_{Refer}$ value (mean ± SD) of 88.0 ± 7.7%, an absolute error (mean ± SD) of 2.14 ± 1.75% and a Pearson's correlation coefficient of 0.94 ($P < 0.01$) were exhibited between $SE_{Predi}$ and $SE_{Refer}$.

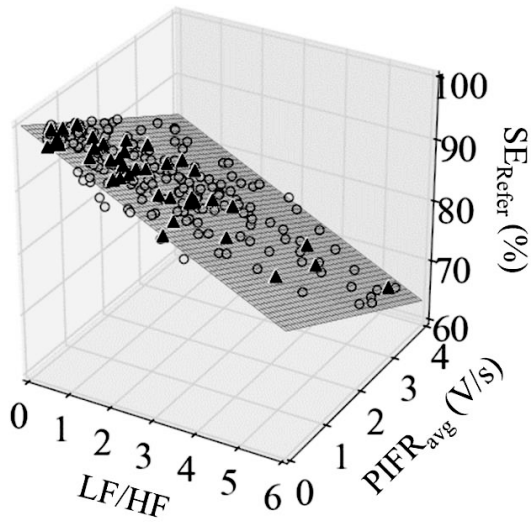



**Figure 2-3.** Representation of the regression model (gray plane) that provided the smallest *k*-fold cross-validation error for the sleep efficiency prediction (training data, hollow circles; validation data, filled triangles). The two predictors of the sleep efficiency measured with polysomnography ($SE_{Refer}$) are LF/HF, which corresponds to the ratio between the power of the heart rate variability low-frequency (LF) band (0.04−0.15 Hz) and that of the high-frequency (HF) band (0.15−0.4 Hz), and $PIFR_{avg}$, which denotes the average peak inspiratory flow rate.

**Table 2-3.** Parameters of the regression model for sleep efficiency prediction

| | Unstandardized coefficient ($B$) | Standardized coefficient ($\beta$) | Adjusted coefficient of determination ($R^2$) |
|---|---|---|---|
| Constant | 100.14 | - | |
| LF/HF | −3.39 | −0.55 | 0.84 |
| $PIFR_{avg}$ (V/s) | −4.11 | −0.43 | |

LF/HF, ratio between the power of the heart rate variability low-frequency (LF) band (0.04−0.15 Hz) and that of the high-frequency (HF) band (0.15−0.4 Hz); $PIFR_{avg}$, average peak inspiratory flow rate.

Table 2-4 summarizes the statistics of LF/HF and $PIFR_{avg}$ in the low- and high-SE groups. Compared with the low-SE group, significantly lower LF/HF and $PIFR_{avg}$ values were observed in the high-SE group (independent samples *t*-test, all $P < 0.001$).

Figure 2-4 shows the relationships between $SE_{Refer}$ and the predictors. The Pearson's correlation coefficient obtained between $SE_{Refer}$ and LF/HF was −0.87 ($P < 0.01$) (Figure 2-4(a)), and that obtained between $SE_{Refer}$ and $PIFR_{avg}$ was −0.86 ($P < 0.01$) (Figure 2-4(b)).

**Table 2-4.** Difference in sleep efficiency predictor values between the two groups

| | Low-SE group | High-SE group | *P*-value |
|---|---|---|---|
| LF/HF | 3.09 ± 1.17 | 1.16 ± 0.74 | < 0.001 |
| $PIFR_{avg}$ (V/s) | 2.31 ± 0.76 | 1.18 ± 0.53 | < 0.001 |

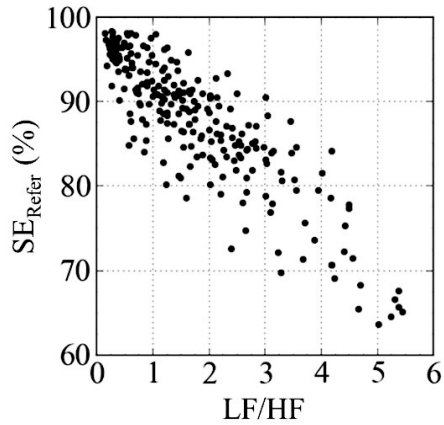
SE, sleep efficiency; LF/HF, ratio between the power of the heart rate variability low-frequency (LF) band (0.04−0.15 Hz) and that of the high-frequency (HF) band (0.15−0.4 Hz); $PIFR_{avg}$, average peak inspiratory flow rate.

The low- and high-SE groups include the subjects with SE < 85% and SE ≥ 85%, respectively.

Data are presented as the mean ± SD.

*P*-values were computed from independent samples *t*-tests.

(a)




(b)

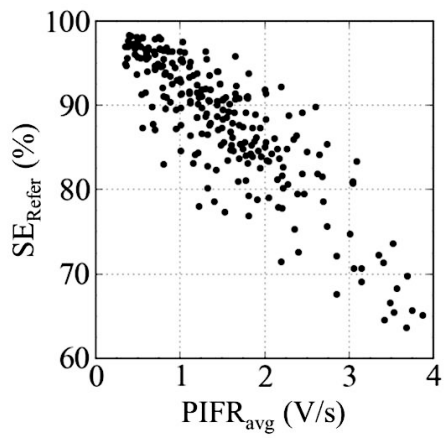



**Figure 2-4.** Scatter plots showing the relationships between the sleep efficiency measured with polysomnography ($SE_{Refer}$, displayed on *y*-axis) and the predictors. LF/HF, which is displayed on the *x*-axis of (a), denotes the ratio between the power of the heart rate variability low-frequency (LF) band (0.04−0.15 Hz) and that of the high-frequency (HF) band (0.15−0.4 Hz). $PIFR_{avg}$, which is displayed on the *x*-axis of (b), corresponds to the average peak inspiratory flow rate.

Table 2-5 reveals the lack of significance in the correlations between the SE predictors and AHI, PLMSI, hypertension, diabetes, angina, arrhythmia, or hyperlipidemia ($P > 0.05$ for all correlation coefficients).

Figure 2-5(a) displays the box-and-whisker plots of LF/HF and the ratio between the HRV LF and HF band powers obtained during each sleep stage. Figure 2-5(b) shows the box-and-whisker plots of $PIFR_{avg}$ and the average peak inspiratory flow rate acquired from the normal breaths in each sleep stage. As shown in Figure 2-5(a), the ratios between the HRV LF and HF band powers obtained during non-rapid eye movement sleep stage 1 (stage N1), stage 2 (stage N2), stage 3 (stage N3), and the rapid eye movement sleep stage (stage R) ($LF/HF_{N1}$, $LF/HF_{N2}$, $LF/HF_{N3}$, and $LF/HF_{R}$, respectively) exhibited significant differences to LF/HF (paired samples t-tests, all $P < 0.001$). The averages of the peak inspiratory flow rates acquired during stage N1, N2, N3, and R ($PIFR_{avg\_N1}$, $PIFR_{avg\_N2}$, $PIFR_{avg\_N3}$, and $PIFR_{avg\_R}$, respectively) exhibited significant differences to $PIFR_{avg}$ (paired samples *t*-tests, all $P < 0.001$), as shown in Figure 2-5(b).

**Table 2-5.** Correlation coefficients between sleep efficiency predictors and clinical features

| | Correlation coefficient | |
|---|---|---|
| | LF/HF | $PIFR_{avg}$ |
| AHI | 0.12 | 0.13 |
| PLMSI | 0.02 | 0.03 |
| Hypertension | 0.13 | 0.09 |
| Diabetes | 0.09 | 0.07 |
| Angina | 0.06 | 0.03 |
| Arrhythmia | 0.11 | 0.09 |
| Hyperlipidemia | 0.07 | 0.11 |

LF/HF, ratio between the power of the heart rate variability low-frequency (LF) band (0.04−0.15 Hz) and that of the high-frequency (HF) band (0.15−0.4 Hz); $PIFR_{avg}$, average peak inspiratory flow rate; AHI, apnea-hypopnea index; PLMSI, periodic limb movements in sleep index.

Pearson's correlation coefficients were calculated for the AHI and PLMSI, and point-biserial correlation coefficients were computed for the others.

*P*-values for all correlation coefficients exceeded 0.05, denoting the lack of significance.

(a) (b)

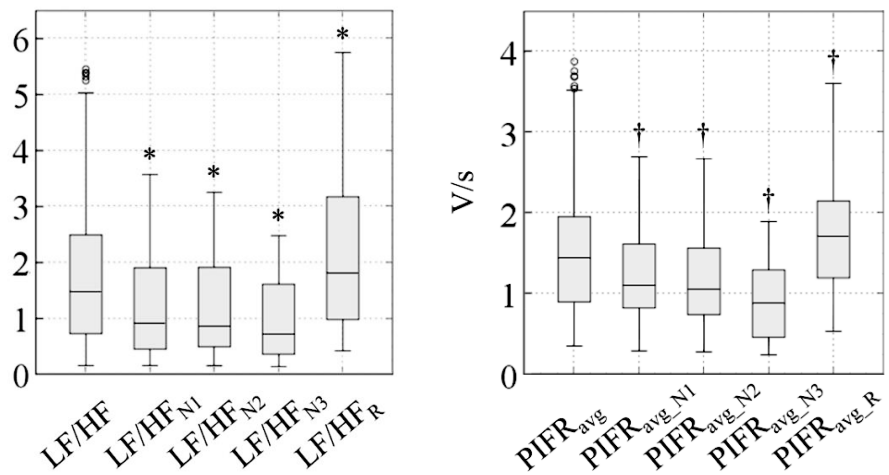



**Figure 2-5.** Box-and-whisker plots showing the 1st to 3rd quartile range (boxes) with the median (horizontal lines in the boxes), the highest and lowest values within 1.5 times of the interquartile range (whiskers outside the boxes), and the outliers (circles). (a) The ratios between the power of the heart rate variability low-frequency (LF) band (0.04−0.15 Hz) and that of the high-frequency (HF) band (0.15−0.4 Hz) obtained before sleep (LF/HF) and during non-rapid eye movement sleep stage 1 (stage N1), stage 2 (stage N2), stage 3 (stage N3), and rapid eye movement sleep stage (stage R) ($LF/HF_{N1}$, $LF/HF_{N2}$, $LF/HF_{N3}$, and $LF/HF_{R}$, respectively). (b) The averages of the peak inspiratory flow rates acquired before sleep ($PIFR_{avg}$) and during stage N1, N2, N3, and R ($PIFR_{avg\_N1}$, $PIFR_{avg\_N2}$, $PIFR_{avg\_N3}$, and $PIFR_{avg\_R}$, respectively). The asterisks and daggers indicate statistically significant differences compared with LF/HF and $PIFR_{avg}$, respectively (paired samples *t*-test, $P < 0.001$).

### 2.3.3. Sleep efficiency prediction model evaluation

The ability of the developed regression model to predict SE could be described with an absolute error (mean ± SD) of 2.18 ± 1.61% and a Pearson's correlation coefficient of 0.94 ($P < 0.01$) between $SE_{Predi}$ and $SE_{Refer}$.

Table 2-6 shows that there are no significant differences in absolute error between $SE_{Predi}$ and $SE_{Refer}$ among the four following groups: the subjects without sleep apnea and PLMS (Group I in Table 2-6); the patients without sleep apnea but with PLMS (Group II in Table 2-6); the patients with sleep apnea but without PLMS (Group III in Table 2-6); and the patients with sleep apnea and PLMS (Group IV in Table 2-6).

Figure 2-6 shows the Bland-Altman plot of the difference between $SE_{Predi}$ and $SE_{Refer}$ against the average of $SE_{Predi}$ and $SE_{Refer}$. The mean of the differences (Figure 2-6, solid line) was 0.06%, and the 95% limits of agreement (Figure 2-6, dashed lines) were observed from −5.28 to 5.40%.

Table 2-7 summarizes the SE classification performance evaluated at SE cut-off values of ≥ 65, 75, 85, and 95%. The averages for the four different SE cut-off values were as follows: sensitivity, 97.1%; specificity, 92.0%; positive predictive value (PPV), 96.7%; negative predictive value (NPV), 97.6%; accuracy, 97.9%; Cohen's kappa coefficient, 0.90, corresponding to almost perfect agreement; and area under the receiver operating characteristics curve (ROC-AUC), 0.99.

**Table 2-6.** Sleep efficiency prediction performance in the four groups

| | Group I | Group II | Group III | Group IV |
|---|---|---|---|---|
| Number of subjects | 27 | 3 | 25 | 5 |
| AHI (events/h) | 2.93 ± 1.65 | 2.69 ± 1.34 | 28.45 ± 16.39*† | 36.07 ± 15.25*† |
| PLMSI (events/h) | 0.96 ± 2.31 | 21.39 ± 4.69* | 1.04 ± 1.46† | 25.49 ± 0.98*‡ |
| $SE_{Refer}$ (%) | 88.83 ± 8.15 | 86.36 ± 6.62 | 86.78 ± 8.74 | 84.78 ± 9.32 |
| Absolute error of SE prediction (%) | 2.18 ± 1.91 | 2.18 ± 1.76 | 2.18 ± 1.41 | 2.19 ± 1.04 |

AHI, apnea-hypopnea index; PLMSI, periodic limb movements in sleep (PLMS) index; $SE_{Refer}$, sleep efficiency (SE) measured with polysomnography.

Groups I, II, III, and IV include the subjects without sleep apnea and PLMS (AHI < 5 events/h and PLMSI < 15 events/h), without sleep apnea but with PLMS (AHI < 5 events/h and PLMSI ≥ 15 events/h), with sleep apnea but without PLMS (AHI ≥ 5 events/h and PLMSI < 15 events/h), and with sleep apnea and PLMS (AHI ≥ 5 events/h and PLMSI ≥ 15 events/h), respectively. Data are presented as the mean ± SD.

*$P$ < 0.05 in comparison to Group I; †$P$ < 0.05 in comparison to Group II; ‡$P$ < 0.05 in comparison to Group III (Mann-Whitney test).

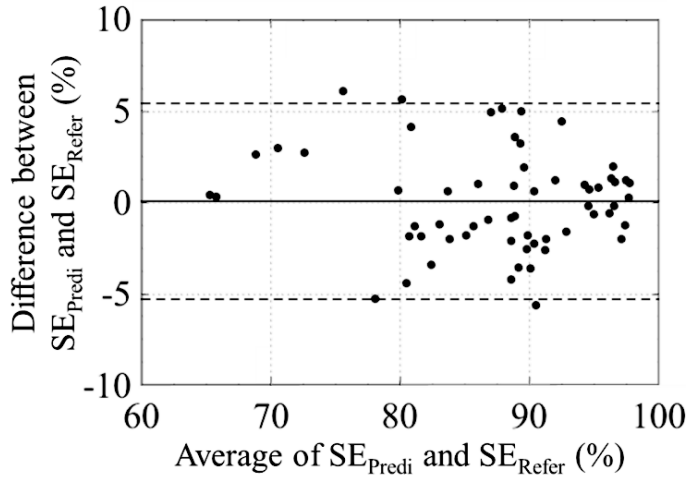



**Figure 2-6.** Bland-Altman plot of the differences between the sleep efficiency predictive values obtained by the developed model ($SE_{Predi}$) and the sleep efficiency reference values measured with polysomnography ($SE_{Refer}$) against the averages of $SE_{Predi}$ and $SE_{Refer}$. The solid line represents the mean of the differences between $SE_{Predi}$ and $SE_{Refer}$, and the dashed lines denote the 95% limits of agreement (± 2*SD of the differences).

**Table 2-7.** Sleep efficiency classification performance

| | SE cut-off (%) | | | |
|---|---|---|---|---|
| | ≥ 65 | ≥ 75 | ≥ 85 | ≥ 95 |
| Sensitivity (%) | 100.0 | 100.0 | 97.6 | 90.9 |
| Specificity (%) | - | 83.3 | 94.7 | 98.0 |
| PPV (%) | 100.0 | 98.2 | 97.6 | 90.9 |
| NPV (%) | - | 100.0 | 94.7 | 98.0 |
| Accuracy (%) | 100.0 | 98.3 | 96.7 | 96.7 |
| Cohen's kappa coefficient | - | 0.90 | 0.92 | 0.89 |
| ROC-AUC | - | 0.99 | 0.98 | 0.99 |

SE, sleep efficiency; PPV, positive predictive value; NPV, negative predictive value; ROC-AUC, area under the receiver operating characteristics curve.

Cohen's kappa coefficients ranging from 0.81 to 1.00 indicate almost perfect agreement.

## 2.4. Discussion

This study hypothesized that the neurophysiological state observed before sleep could be associated with SE. To assess autonomic activity, HRV and breathing parameters were analyzed for 5 min during the awake resting period. The duration of the parameter observation corresponded to the minimum time that could provide meaningful information with respect to the HRV frequency-domain parameters. The most effective SE predictors were determined to be LF/HF and $PIFR_{avg}$, which exhibited strong negative correlations with SE. According to the Sobel test, which validated the mediation effect of LF/HF on the relationship between $PIFR_{avg}$ and SE ($z$ = −2.187, $P$ = 0.029), LF/HF and $PIFR_{avg}$ might contribute to predicting SE as the result and the cause of sympathetic activation, respectively [61]. A faster inspiratory flow rate causes a greater increase in carbon dioxide concentrations in the body per unit time, which produces stronger sympathetic nervous system activation to exhaust carbon dioxide. The enhanced sympathetic activation results in the dominance of the HRV LF band power over the HF band power.

The use of short data acquisition time and unconstrained physiological signal measurement contribute to improving the efficiency and usability of the proposed method. In terms of applicability, the method can be used to predict the TST when TRT information is available. For Dataset II, with an average TRT of 514 min, the MAE of SE produced by the proposed method

is 2.18%, translating into an MAE of 11.21 min for the TST. Independent validations of SE prediction performance, which were conducted not only by subjects without sleep disorders but also by patients with sleep apnea or PLMS, showed the wide applicability of the developed model.

This is the first study to develop a strategy to provide SE predictive values during the awake resting period. Several previous studies have attempted to estimate SE without the use of PSG, although they required constrained overnight recording. Table 2-8 summarizes the performance of previously reported SE estimations. This review does not include studies that used subjects in categories not considered in this study (e.g., elderly individuals with a mean age of greater than 80 years, intellectually disabled subjects with motor handicaps, and depression patients). For comparison, the SE estimation performance of the proposed method is also displayed in the last row of Table 2-8. Most of the existing SE estimation methods are based on actigraphy. The application of actigraphy in sleep research is useful because it is less cumbersome and less expensive than PSG and easily collects long-term recordings in the participants' usual sleeping environments [62]. However, wearing an activity monitoring device can cause discomfort and sleep disturbance [63]. A critical limitation of the use of actigraphy for SE estimation is the high possibility of overestimating the time spent sleeping due to the user lying in bed awake but motionless for long periods [64]. It is notable that although the proposed method is not based on whole-night

recording, it exhibited better performance compared to existing methods. An SE < 85% is a commonly used quantitative criterion for the objective determination of insomnia [65]. As shown in Table 2-7, the developed model exhibited an acceptable performance in terms of sensitivity (97.6%) and specificity (94.7%) for the dichotomous classification of SE values with a cut-off of ≥ 85%.

**Table 2-8.** Comparison of the performance of sleep efficiency estimation methods

| Reference | Tool | Number of subjects | ME (%) | MAE (%) | Correlation coefficient |
|---|---|---|---|---|---|
| Jean-Louis *et al.*, 2001 [66] | Actigraph (Actillume I, SUMACT mode) | 5 (each spent 5 nights) | −1 | - | 0.67 |
| | Actigraph (Actillume I, MAXACT mode) | | 2 | - | 0.69 |
| | Actigraph (Mini Motionlogger, Zero-Crossing Mode) | | −2 | - | 0.55 |
| | Actigraph (Mini Motionlogger, Time-Above-Threshold Mode) | | −1 | - | 0.57 |
| | Actigraph (Mini Motionlogger, Proportional-Integrating Mode) | | 0 | - | 0.87 |
| de Souza *et al.*, 2003 [67] | Actigraph (Mini Motionlogger, Cole's algorithm) | 21 | 4.0 | - | 0.39 |
| | Actigraph (Mini Motionlogger, Sadeh's algorithm) | | 2.0 | - | 0.41 |
| Rupp & Balkin, 2011 [68] | Actigraph (Basic Mini-Motionlogger) | 29 | 7.69 | - | - |
| | Actigraph (Actiwatch-L) | | 4.41 | - | - |
| Adnane *et al.*, 2012 [69] | Single-lead ECG | 14 SE < 85<br>4 SE ≥ 85 | - | 4.64 | - |
| Sharif & BaHammam, 2013 [70] | BodyMedia's senseWear™ armband | 107 OSA patients | - | - | 0.52 |
| | | 30 control | - | - | 0.56 |
| Jung *et al.* (this study) | ECG and thoracic volume change signal | 12 SE < 85<br>28 SE ≥ 85 | 0.07 | 2.14 | 0.94 |
| | PVDF film sensor signal | 19 SE < 85<br>41 SE ≥ 85 | 0.05 | 2.18 | 0.94 |

ME, mean error; MAE, mean absolute error; ECG, electrocardiogram; SE, sleep efficiency; OSA, obstructive sleep apnea; PVDF, polyvinylidene fluoride.

Many previous studies have observed and analyzed HRV and breathing parameters in normal and pathological sleep, and the results showed the suitability of these parameters to estimate sleep architecture [71] and detect associated events (e.g., cyclic alternating pattern [72], PLMS [73], sleep bruxism [74], and obstructive sleep apnea [75]). It is an innovative attempt of this study to extend the range of the clinical application of HRV and breathing parameters in sleep research by utilizing them for SE prediction.

The proposed method has the potential to facilitate home-based, long-term monitoring of night-to-night SE variability. This could be useful for early detection of SE-lowering causes by helping clinical decision-making regarding the need and urgency for formal PSG, thus decreasing the risk of complications produced by an untreated low SE.

The proposed method can potentially be applied to provide helpful information to establish effective SE improvement strategies. Many approaches have been suggested to increase SE. Primary recommendations for better SE include modifications of behavioral practices associated with napping, exposure to light, exercise, and bathing; with the intake of nicotine, alcohol, and caffeinated foods and beverages (e.g., tea, coffee, cola, and chocolate) near bedtime; and with the use of the bed to watch television, listen to the radio, and read books [76-78]. Additionally, automatic systems for controlling the sleep environment have been developed based on the effects of the bedroom environment (including the air temperature, relative humidity,

indoor air quality, illumination, and noise) on the SE [79-84]. Neurofeedback and biofeedback training have also been suggested as assistive tools for improving SE [85-87]. Prior to applying these SE improvement strategies, providing a predictive SE value could assist effective decision-making regarding the necessary strictness and intensity of their implementation.

This study has limitations associated with generalizability and reproducibility. Further validation of the proposed method using external datasets, especially using at-home, multi-night recordings, is required. Considering the bi-directional relationship between sleep and ANS activity, the extraction of effective SE predictors from the sleep health information of the previous night and their incorporation into the developed model will be investigated in future work as a strategy for improving the SE predictability.

# Chapter 3. Apnea-Hypopnea Index Prediction

## 3.1. Hypothesis

To obtain effective predictors of the AHI in OSA patients, two hypotheses were proposed. The first hypothesis was that the difference in AHI would be reflected in the irregularity of the respiration cycles observed during the sleep-wake transition period. This hypothesis was based on the following studies. During the sleep-wake transition period, repeated fluctuations between the sleep and wakefulness states are observed and the transition from wakefulness to sleep (or from sleep to wakefulness) is associated with relative hypoventilation (or hyperventilation), which causes an increase (or decrease) in arterial $pCO_2$ (carbon dioxide partial pressure) [88]. The arterial $pCO_2$ is known as a stimulator of the ANS. In non-OSA subjects, active and sensitive responses of the ANS to alternate stimulation during the sleep-wake transition period would result in irregular respiration cycles. On the other hand, OSA patients' unresponsive ANS to the stimulation due to autonomic dysfunction would cause regular respiration cycles. Autonomic dysfunction in OSA patients is known to be associated with nocturnal hypoxemia [89]. More frequent nocturnal hypoxemia is expressed as a higher AHI value. Taken together, it was also possible to hypothesize that higher AHI values might be related to more severe autonomic dysfunction, which could cause less irregular respiration cycles during the sleep-wake transition period.

The second hypothesis was that patients with more severe OSA would

exhibit greater attenuation of the waking vagal tone, which could result in lower effectiveness in decreasing heart rate (HR) as a response to deep inspiration breath-holding (DIBH). This hypothesis was based on the following previous findings. DIBH can trigger a diving response, whose primary role is to conserve oxygen for sensitive brain and heart tissue and to delay the onset of serious hypoxic damage. This leads to a reduction of the HR through vagal activation and peripheral vasoconstriction in the arterial vascular tree [90]. Untreated OSA patients are at increased risk of cardiovascular diseases, such as hypertension [91], myocardial ischemia [92], myocardial infarction [93], and heart failure [94]. These cardiac pathological conditions are caused by abnormal autonomic nervous function, specifically by vagal downregulation, resulted from the repetitive OSA-induced hypoxemia [95]. In summary, a decrease in the HR would not be an ordinary physiological response to DIBH in severe OSA patients with impaired autonomic function.

## 3.2. Methods

### 3.2.1. Datasets

Two different datasets were used in this study. The first one, designated as Dataset III, was organized to verify the study hypotheses using reference cardiorespiratory signals. This dataset included polysomnographic recordings collected from 120 subjects who had undergone diagnostic overnight PSG at

the Center for Sleep and Chronobiology of Seoul National University Hospital between July 2012 and January 2013 because of suspected OSA. The second dataset, designated as Dataset IV, was constructed to assess the practical applicability of the study hypotheses using unobtrusively measured cardiorespiratory signals. This dataset consisted of 30 subjects who had undergone overnight PSG at the Center for Sleep and Chronobiology of Seoul National University Hospital between July 2012 and October 2013 because of suspected OSA. The suspected OSA patients were identified by a sleep physician in accordance with the Berlin questionnaire.

The physiological parameters acquired during the PSG to determine the type and severity of SRBD were as follows: nasal pressure, measured using a nasal cannula/pressure transducer (PTAF2, Pro-Tech Services Inc., Mukilteo, Washington, USA); oronasal airflow, acquired using a thermocouple (Compumedics Ltd., Victoria, Australia); thoracic and abdominal volume changes, measured with piezoelectric-type belts (zRIP DuraBelt, Pro-Tech Services Inc., Mukilteo, Washington, USA); blood oxygen saturation, determined using a pulse oximeter (MARS, type 2001, Respironics Novametrix Inc., Murrysville, Pennsylvania, USA); and snoring sound, acquired with 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 AASM manual. A respiratory event was classified as apnea when it met both of the following

criteria: 1) a drop in the peak signal excursion of an oronasal thermal sensor by ≥ 90% of the pre-event baseline, and 2) this occurring with a duration of ≥ 10 s [4]. A respiratory event was categorized as hypopnea when it met all of the following criteria: 1) a peak signal excursion drop by ≥ 30% of the pre-event baseline determined using nasal pressure; 2) this occurring with a duration of ≥ 10 s; and 3) a ≥ 3% oxygen desaturation from the pre-event baseline or the event is associated with an arousal [4]. The number of apnea and hypopnea events per hour of sleep was designated as $AHI_{Refer}$, denoting the AHI reference value.

In both datasets, the subjects were classified as non-OSA ($AHI_{Refer} < 5$ events/h) subjects, and mild OSA ($5 \leq AHI_{Refer} < 15$ events/h), moderate OSA ($15 \leq AHI_{Refer} < 30$ events/h), and severe OSA ($AHI_{Refer} \geq 30$ events/h) patients. The four groups in each dataset were consistent regarding gender ratio and age.

The exclusion criteria for both datasets were the following: 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 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 mmHg and/or diastolic BP ≥ 90 mmHg.

The Institutional Review Board of Seoul National University Hospital approved this retrospective study and waived the patient consent requirement (IRB No. 1405-075-581 and No. 1603-127-750).

The demographic and anthropometric characteristics and sleep-related parameters of Datasets III and IV are summarized in Table 3-1 and Table 3-2, respectively.

**Table 3-1.** Demographic and anthropometric characteristics and sleep-related parameters of the subjects in Dataset III

| | Non-OSA | Mild OSA | Moderate OSA | Severe OSA |
|---|---|---|---|---|
| Number of subjects (male/female) | 22 (17/5) | 33 (26/7) | 35 (28/7) | 30 (24/6) |
| Age (years) | 43.2 ± 12.1 | 42.8 ± 13.7 | 43.3 ± 12.9 | 43.5 ± 14.6 |
| BMI ($kg/m^2$) | 23.5 ± 3.8 | 24.2 ± 3.5 | 24.7 ± 4.1 | 25.4 ± 4.0 |
| TRT (min) | 499.5 ± 44.6 | 494.3 ± 35.8 | 496.2 ± 38.2 | 489.7 ± 39.0 |
| SE (%) | 88.5 ± 10.4 | 86.8 ± 10.2 | 87.7 ± 9.5 | 86.9 ± 9.7 |
| $AHI_{Refer}$ (events/h) | 2.3 ± 1.6 | 9.7 ± 3.1* | 21.1 ± 4.0*† | 52.3 ± 18.2*†‡ |

OSA, obstructive sleep apnea; BMI, body mass index; TRT, total recording time; SE, sleep efficiency; $AHI_{Refer}$, apnea-hypopnea index measured with polysomnography.

Subjects were classified according to their $AHI_{Refer}$ values into the non-OSA ($AHI_{Refer} < 5$ events/h), mild OSA ($5 \leq AHI_{Refer} < 15$ events/h), moderate OSA ($15 \leq AHI_{Refer} < 30$ events/h), and severe OSA ($AHI_{Refer} \geq 30$ 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 (Mann-Whitney test).

**Table 3-2.** Demographic and anthropometric characteristics and sleep-related parameters of the subjects in Dataset IV

| | Non-OSA | Mild OSA | Moderate OSA | Severe OSA |
|---|---|---|---|---|
| Number of subjects (male/female) | 5 (5/0) | 8 (5/3) | 9 (6/3) | 8 (5/3) |
| Age (years) | 42.6 ± 7.2 | 43.1 ± 6.9 | 43.2 ± 7.4 | 43.4 ± 6.8 |
| BMI ($kg/m^2$) | 23.7 ± 3.5 | 24.3 ± 3.3 | 24.6 ± 3.6 | 25.2 ± 3.8 |
| TRT (min) | 496.4 ± 32.5 | 494.2 ± 30.5 | 495.6 ± 35.0 | 490.2 ± 32.3 |
| SE (%) | 88.6 ± 8.4 | 87.3 ± 8.5 | 86.7 ± 8.3 | 86.4 ± 8.2 |
| $AHI_{Refer}$ (events/h) | 2.6 ± 1.6 | 9.3 ± 3.2* | 20.8 ± 4.0*† | 52.2 ± 18.8*†‡ |

OSA, obstructive sleep apnea; BMI, body mass index; TRT, total recording time; SE, sleep efficiency; $AHI_{Refer}$, apnea-hypopnea index measured with polysomnography.

Subjects were classified according to their $AHI_{Refer}$ values into the non-OSA ($AHI_{Refer} < 5$ events/h), mild OSA ($5 \leq AHI_{Refer} < 15$ events/h), moderate OSA ($15 \leq AHI_{Refer} < 30$ events/h), and severe OSA ($AHI_{Refer} \geq 30$ 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 (Mann-Whitney test).

### 3.2.2. Experimental procedure

Between 5 min to 30 min prior to PSG, each subject performed an experiment that consisted of two consecutive sessions. The first was a baseline measurement session, during which spontaneous and habitual breathing was observed for 60 s with the subject in the supine position. This was immediately followed by the second, breath-holding session, during which the subject was instructed to perform DIBH for 15 s while remaining in the supine position. All subjects were required to avoid exercise, nicotine, alcohol, and caffeinated foods and beverages for an hour prior to the experiment.

During the experiment, the 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 correct performance of DIBH. In addition to these signals, piezoelectric sensor signals were measured for the subjects in Dataset IV using the PVDF film sensor array, presented in Figure 2-1.

### 3.2.3. Data analysis

Band-pass (0.5–35 Hz) and low-pass (0.5 Hz) filters were applied to the ECG and nasal pressure signals, respectively. Each of the piezoelectric sensor signals was band-pass (0.5–20 Hz) filtered to obtain a BCG. Low-frequency

fluctuations in the piezoelectric sensor signals corresponding to respiratory effort signals were acquired by low-pass (0.5 Hz) filtering.

After the detection of R peaks in the filtered ECG and J peaks in the BCG, NN intervals were obtained from the time series data of the RR and JJ intervals. Outliers caused by false or missed peak detections were identified by a sliding window filter with a length of 2,501 data points. The NN intervals, acquired by removing central points lying outside 20% of the window average, were used to calculate the HR values.

### 3.2.3.1. Predictor extraction

*$RESP_{CV}$*

The first predictor was the CV of the respiration cycles acquired during the sleep-wake transition period, designated as $RESP_{CV}$ and calculated as follows:

$$\mathrm{RESP_{CV}}\ (\%) = \frac{\mathrm{RESP_{SD}}}{\mathrm{RESP_{avg}}} \times 100$$

where $RESP_{SD}$ and $RESP_{avg}$ are the SD and average of the respiration cycles obtained during the sleep-wake transition period, respectively. To determine the respiration cycles during the sleep-wake transition period, the following methods were employed.

*Sleep-wake transition period detection*

Sleep-wake transitions are observed near the sleep-onset. In the 2012 AASM manual, the sleep-onset is defined as the time required to reach the

first epoch of any sleep stage other than wakefulness. The gold standard method for classifying sleep stages requires electroencephalographic, electrooculargraphic, and electromyographic monitoring. In this study, the sleep-onset was determined using the HR data because of their easy availability. The algorithm for identifying the sleep-onset was designed based on the significantly slower HR exhibited during sleep compared with that observed during wakefulness [96]. Figure 3-1 presents the flow chart used to determine a sleep-onset epoch. Prior to applying the process shown in Figure 3-1, the threshold (TH) was calculated as follows:

$$\mathrm{TH} = \mathrm{HR2}_{\mathrm{avg}} - 1.96 \times \mathrm{HR2}_{\mathrm{SD}}$$

where $HR2_{avg}$ and $HR2_{SD}$ are the average and SD of the collected HR samples, respectively. These values were calculated from the HR samples acquired in the first 2 min of recording (from the 1st to 4th epoch), after removing the outliers (values exceeding ± 1.96*SD). Starting from the 5th epoch, the HR samples in each consecutive epoch were examined one-by-one until a sleep-onset epoch was identified. When the number of successive HR samples below TH was greater than half of the total number of HR samples in the epoch, the epoch was determined as a sleep-onset epoch. The sleep-wake transition period was defined as a period containing a sleep-onset epoch, the two previous, and the two next epochs (e.g., if the sleep-onset epoch is the 6th epoch, the sleep-wake transition period includes from 4th to 8th epoch, ranging from 90 to 240 s).

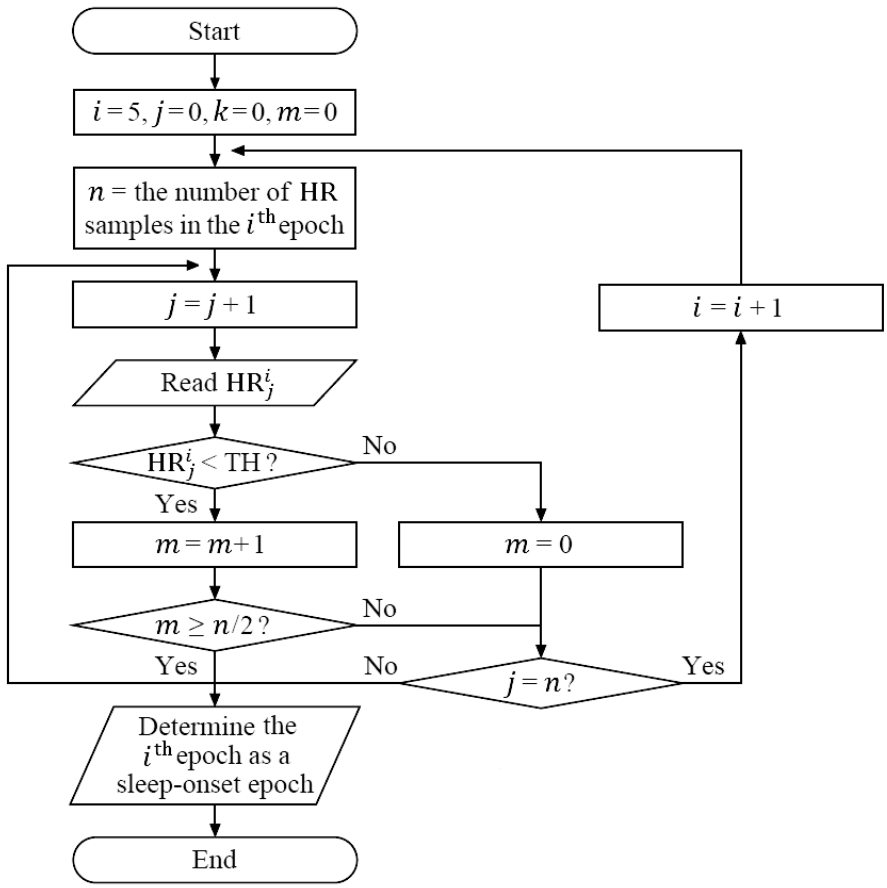



**Figure 3-1.** Flow chart used to determine a sleep-onset epoch. HR and TH denote the heart rate and threshold, respectively. $\text{HR}_j^i$ indicates the value of the $j^{\text{th}}$ HR sample in the $i^{\text{th}}$ epoch.

*Respiration cycle detection*

For Dataset III, the ECG-derived respiration (EDR) signals were acquired by summing the magnitudes in an R-peak-centered window of 100 ms (from 50 ms before the R peak to 50 ms after the R peak) [97]. In the sinusoidal waveforms of the EDR signals, the time interval between two successive maximum peaks was defined as a respiration cycle.

For Dataset IV, the respiration cycle was obtained by calculating the time interval between two successive maximum peaks in the respiratory effort signals, which were derived from the piezoelectric sensor signals.

*RMSSD*

The second predictor was the RMSSD over the entire period of the experiment. The RMSSD was used to evaluate the waking vagal activation and computed as follows:

$$\mathrm{RMSSD}\ \ (\mathrm{ms}) = \sqrt{\frac{\sum_{i=1}^{n-1}(NN_{i+1} - NN_i)^2}{n-1}}$$

where $NN_i$ is the $i^{th}$ NN interval and n is the total number of NN intervals examined during the experiment.

*$HR_{VR}$*

The third predictor was the HR variation ratio ($HR_{VR}$), which was used to assess the vagal influence on the decrease in HR during DIBH. The $HR_{VR}$

was calculated as follows:

$$\mathrm{HR_{VR}}\ (\%) = \frac{\mathrm{mHR_{BL}} - \mathrm{mHR_{BH}}}{\mathrm{mHR_{BL}}} \times 100$$

where $\mathrm{mHR_{BL}}$ and $\mathrm{mHR_{BH}}$ are the mean values of the HR data acquired during the baseline measurement and breath-holding sessions, respectively. To counteract the effect of inter-individual variability, the ratio was considered instead of the difference.

### 3.2.3.2. Statistical analysis

Prior to developing AHI prediction models, the performances of the methods employed to detect the sleep-wake transition period and the respiration cycles were assessed.

Three AHI prediction models were developed using the suggested predictors obtained from Dataset III. Model I was established using $\mathrm{RESP_{CV}}$. The RMSSD and $\mathrm{HR_{VR}}$ values were used to construct Model II. Model III was developed using $\mathrm{RESP_{CV}}$, RMSSD, and $\mathrm{HR_{VR}}$. Regression analysis was employed to establish each AHI prediction model and *k*-fold cross-validation testing was applied to avoid overfitting problems. The AHI predictability of each regression model was evaluated using Dataset IV.

CurveExpert Professional software (v.2.0.4, http://www.curveexpert.net/, USA) was used to perform regression analyses with a significant probability level of 95%. The other statistical analyses were performed using SPSS statistics software (v.21.0, SPSS Inc., Chicago, Illinois, USA).

## 3.3. Results

### 3.3.1. Apnea-hypopnea index predictor extraction

From the PSG recordings obtained in this study, stage R was not observed in the sleep-onset and the two next epochs.

The difference between the sleep-wake transition period derived from the PSG results and that detected by the proposed method was evaluated using a correct detection rate (CDR). CDR was defined as the percentage of the number of epochs correctly detected as the epochs composing the sleep-wake transition period. CDR values (mean ± SD) of 78.8 ± 13.5% and 78.7 ± 16.6%, which denote an epoch-shifted detection on average, were calculated for Datasets III and IV, respectively.

Between the $RESP_{CV}$ obtained from the EDR signals and that acquired from the nasal pressure signals, an absolute error (mean ± SD) of 1.25 ± 1.03% was observed for Dataset III. For Dataset IV, the absolute error (mean ± SD) was 1.23 ± 1.01% between the $RESP_{CV}$ obtained from the respiratory effort signals and that acquired from the nasal pressure signals.

### 3.3.2. Apnea-hypopnea index prediction model development

*Model I (Predictor: $RESP_{CV}$)*

Figure 3-2 displays the respiration cycles obtained from two subjects belonging to different OSA severity groups. Both subjects exhibited high similarity between the nasal pressure signal- and EDR signal-derived respiration cycles. During the 150-s sleep-wake transition period, the non-OSA subject showed relatively irregular respiration cycles (Figure 3-2(a); the $RESP_{CV}$ values calculated from the nasal pressure and EDR signals were 25.5% and 24.7%, respectively). On the other hand, less irregular respiration cycles were observed in the severe OSA patient (Figure 3-2(b); the $RESP_{CV}$ values calculated from the nasal pressure and EDR signals were 7.6% and 8.0%, respectively).

The difference in $RESP_{CV}$ according to OSA severity is represented with the box-and-whisker plot in Figure 3-3. A smaller mean of $RESP_{CV}$ was observed in the more severe OSA group. Concretely, the $RESP_{CV}$ values (mean ± SD) were 25.8 ± 2.9%, 20.5 ± 1.8%, 16.3 ± 2.3%, and 9.8 ± 3.9% in the non-, mild, moderate, and severe OSA groups, respectively. The Kruskal-Wallis test revealed the significance of differences in the $RESP_{CV}$ among the OSA severity groups ($P < 0.001$).

For all subjects, a Spearman's rho of −0.93 ($P < 0.01$) was obtained between $AHI_{Refer}$ and $RESP_{CV}$.

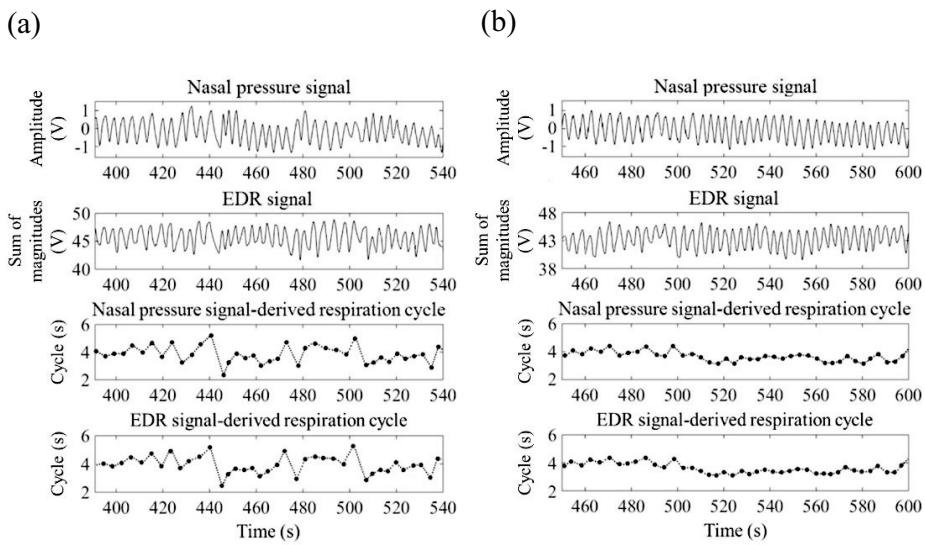



**Figure 3-2.** (a) An illustrative case of respiration cycles obtained from a non-obstructive sleep apnea (OSA) subject, and (b) that obtained from a severe OSA patient. Nasal pressure and electrocardiogram-derived respiration (EDR) signals, and nasal pressure signal- and EDR signal-derived respiration cycles obtained by computing the time intervals between two successive maximum peaks in the nasal pressure and EDR signals, respectively. The time of data acquisition (*x*-axis) corresponds to the 150-s sleep-wake transition period determined by the proposed method.

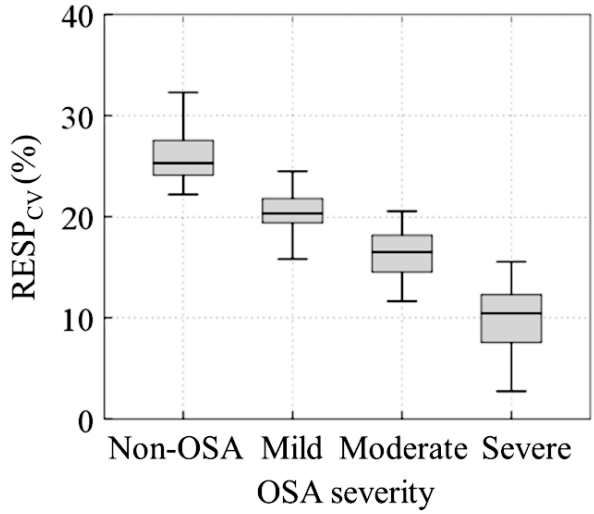



**Figure 3-3.** Box-and-whisker plot showing the 1st to 3rd quartile range (boxes) with the median (bold horizontal lines in the boxes) and the highest and lowest value within 1.5 times of the interquartile range (whiskers outside the boxes). There were significant differences in the coefficient of variation of respiration cycles acquired during the sleep-wake transition period ($RESP_{CV}$) according to the obstructive sleep apnea (OSA) severity (Kruskal-Wallis test, $P < 0.001$).

The statistical results of the regression analyses and the 2-, 4-, and 6-fold cross-validation tests are summarized in Table 3-3. The values of the MAE and Pearson's correlation coefficient in Table 3-3 were computed from the AHI predictive value ($AHI_{Predi}$) and $AHI_{Refer}$.

Figure 3-4 shows the regression model that provided the smallest *k*-fold cross-validation error ($k$ = 2, 4, and 6). The best-fitting curve (Figure 3-4, solid line) to the training data (Figure 3-4, hollow circles) was derived from the rational function. The representation of the regression function is summarized in Table 3-4, along with the $R^2$ value. For the training set including the data of 90 individuals with an $AHI_{Refer}$ value (mean ± SD) of 22.7 ± 21.2 events/h, an absolute error (mean ± SD) of 4.60 ± 3.77 events/h and a Pearson's correlation coefficient of 0.96 ($P < 0.01$) were observed between $AHI_{Predi}$ and $AHI_{Refer}$. For the validation set that consisted of the data of the remaining 30 individuals (Figure 3-4, filled triangles) with an $AHI_{Refer}$ value (mean ± SD) of 21.2 ± 19.9 events/h, an absolute error (mean ± SD) of 4.92 ± 4.05 events/h and a Pearson's correlation coefficient of 0.95 ($P < 0.01$) were exhibited between $AHI_{Predi}$ and $AHI_{Refer}$.

**Table 3-3.** Cross-validation statistics for apnea-hypopnea index predictive models developed using $RESP_{CV}$

| Cross-validation | MAE (%) | | Pearson's correlation coefficient | |
|---|---|---|---|---|
| | Training set | Validation set | Training set | Validation set |
| 2-fold | 4.63 ± 0.51 | 4.82 ± 0.82 | 0.96 ± 0.01 | 0.95 ± 0.02 |
| 4-fold | 4.67 ± 0.31 | 4.81 ± 0.94 | 0.96 ± 0.01 | 0.96 ± 0.02 |
| 6-fold | 4.67 ± 0.22 | 4.74 ± 1.01 | 0.96 ± 0.00 | 0.96 ± 0.02 |

$RESP_{CV}$, coefficient of variation of respiration cycles acquired during the sleep-wake transition period; MAE, mean absolute error.

The values for the MAE and Pearson's correlation coefficient were calculated between the apnea-hypopnea index predictive values and reference values measured with polysomnography.

Data are presented as the mean ± SD.

$P < 0.01$ for all Pearson's correlation coefficients.

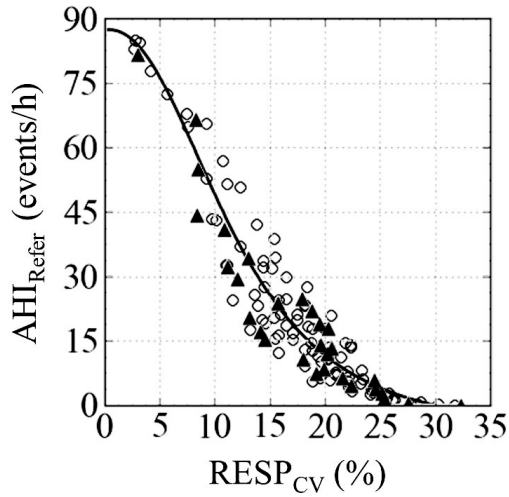



**Figure 3-4.** Regression model (solid line) developed using the apnea-hypopnea index measured with polysomnography ($AHI_{Refer}$, dependent variable) and the coefficient of variation of respiration cycles acquired during the sleep-wake transition period ($RESP_{CV}$, explanatory variable) (training data, hollow circles; validation data, filled triangles).

**Table 3-4.** Parameters of the regression model using $RESP_{CV}$ to predict apnea-hypopnea index

| Variable | | Regression function | $R^2$ |
|---|---|---|---|
| $y$ | $AHI_{Predi}$ (events/h) | $y = \frac{87.52 - 2.91 \times x}{1 - 0.04 \times x + 5.69 \times 10^{-3} \times x^2}$ | 0.92 |
| $x$ | $RESP_{CV}$ (%) | | |

$RESP_{CV}$, coefficient of variation of respiration cycles acquired during the sleep-wake transition period; $AHI_{Predi}$, apnea-hypopnea index predictive value; $R^2$, coefficient of determination.

*Model II (Predictors: RMSSD and $HR_{VR}$)*

For each OSA severity group, the $mHR_{BL}$ and $mHR_{BH}$ statistics are summarized in Table 3-5. There were no significant differences in the $mHR_{BL}$ values among the groups (Mann-Whitney test, all $P > 0.05$). The $mHR_{BH}$ value calculated for the severe OSA group was significantly greater than that calculated for each of the non-, mild, and moderate OSA groups (Mann-Whitney test, $P < 0.05$).

Figure 3-5 shows the simultaneous recordings of the nasal pressure and ECG obtained from two subjects belonging to different OSA severity groups. The 75-s recordings in Figure 3-5 include the signals acquired during the baseline measurement (from 0 to 60 s) and breath-holding (from 60 to 75 s) sessions. The accomplishment of DIBH could be verified from the nasal pressure signals with specific patterns, as shown in Figure 3-5(a) and (b). During DIBH, the non-OSA ($AHI_{Refer}$ = 3.6 events/h) subject showed longer RR intervals (slower HR) than the RR intervals observed during spontaneous and habitual breathing (Figure 3-5(a); RMSSD = 56.0 ms, $mHR_{BL}$ = 68.7 bpm, $mHR_{BH}$ = 61.6 bpm, and $HR_{VR}$ = 10.3%). However, this distinguishable lengthening of the RR intervals compared to the RR intervals produced by spontaneous and habitual breathing was not observed in the severe OSA ($AHI_{Refer}$ = 32.6 events/h) patient (Figure 3-5(b); RMSSD = 22.1 ms, $mHR_{BL}$ = 67.6 bpm, $mHR_{BH}$ = 66.4 bpm, and $HR_{VR}$ = 1.8%).

**Table 3-5.** Heart rate statistics of the subjects

| | Non-OSA | Mild OSA | Moderate OSA | Severe OSA |
|---|---|---|---|---|
| $mHR_{BL}$ (bpm) | 73.2 ± 8.6 | 70.7 ± 9.5 | 70.4 ± 9.0 | 71.8 ± 8.7 |
| $mHR_{BH}$ (bpm) | 65.7 ± 7.5 | 66.4 ± 8.8 | 68.1 ± 8.9 | 71.7 ± 9.2*†‡ |

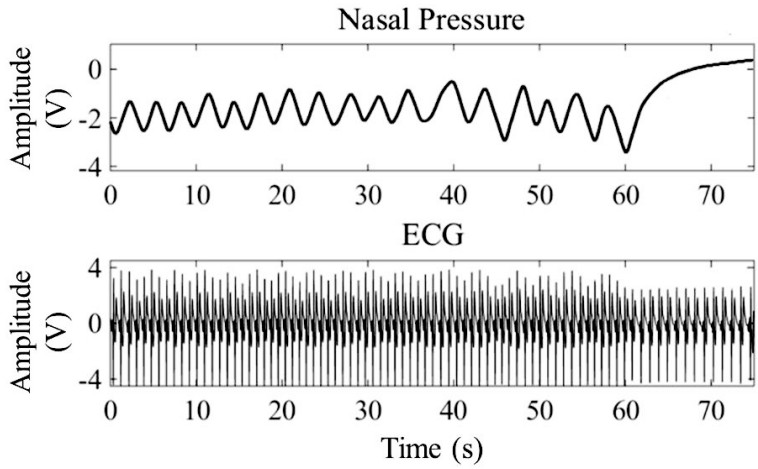
OSA, obstructive sleep apnea; $mHR_{BL}$, mean of heart rate (HR) values acquired during 60-s spontaneous and habitual breathing; $mHR_{BH}$, mean of HR values obtained during 15-s deep inspiration breath-holding.

Subjects were classified according to their apnea-hypopnea index measured with polysomnography ($AHI_{Refer}$) into non-OSA ($AHI_{Refer} < 5$ events/h), mild OSA ($5 \leq AHI_{Refer} < 15$ events/h), moderate OSA ($15 \leq AHI_{Refer} < 30$ events/h), and severe OSA ($AHI_{Refer} \geq 30$ 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 (Mann-Whitney test).

(a)




(b)

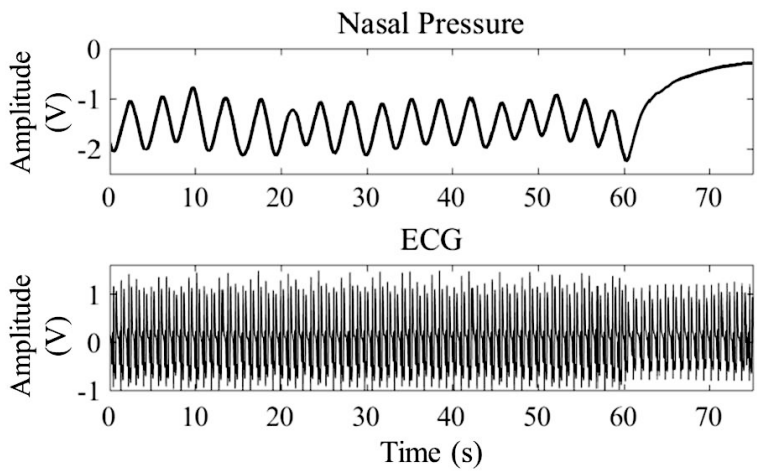



**Figure 3-5.** Simultaneous recordings of nasal pressure and electrocardiogram (ECG). (a) An illustrative case obtained from a non-obstructive sleep apnea (OSA) subject, and (b) that obtained from a severe OSA patient. The signals were acquired during 60-s (from 0 to 60 s) spontaneous and habitual breathing followed by 15-s (from 60 to 75 s) deep inspiration breath-holding.

Figure 3-6 represents the relationships between $AHI_{Refer}$ and the two predictors. Between $AHI_{Refer}$ and RMSSD, a Spearman's rho of −0.94 ($P < 0.01$) was obtained (Figure 3-6(a)). The Spearman's rho calculated between $AHI_{Refer}$ and $HR_{VR}$ was −0.92 ($P < 0.01$) (Figure 3-6(b)).

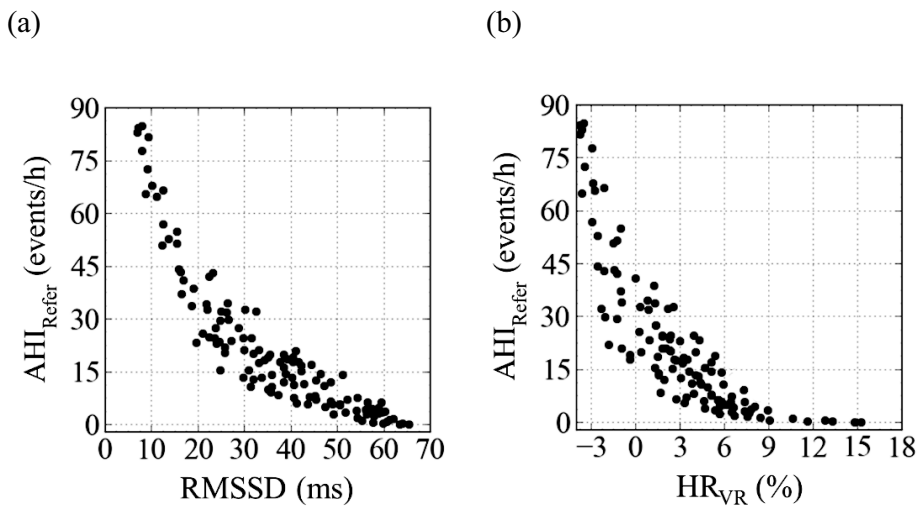



**Figure 3-6.** Scatter plots showing the relationships between the apnea-hypopnea index measured with polysomnography ($AHI_{Refer}$, displayed on the *y*-axis) and the predictors. RMSSD, displayed on the *x*-axis of (a), corresponds to the root mean square of successive normal-to-normal sinus interval differences over the entire period of the experiment. $HR_{VR}$, displayed on the *x*-axis of (b), corresponds to the heart rate (HR) variation ratio calculated by dividing the difference between the mean of HR values acquired during 60-s spontaneous and habitual breathing ($mHR_{BL}$) and that obtained during 15-s deep inspiration breath-holding into the $mHR_{BL}$ (expressed as a percentage).

The statistical results of the regression analyses and 2-, 4-, and 6-fold cross-validation tests are summarized in Table 3-6.

**Table 3-6.** Cross-validation statistics for apnea-hypopnea index predictive models developed using RMSSD and $HR_{VR}$

| Cross-validation | MAE (%) | | Pearson's correlation coefficient | |
|---|---|---|---|---|
| | Training set | Validation set | Training set | Validation set |
| 2-fold | 3.17 ± 0.16 | 3.33 ± 0.17 | 0.98 ± 0.00 | 0.98 ± 0.00 |
| 4-fold | 3.21 ± 0.15 | 3.37 ± 0.26 | 0.98 ± 0.00 | 0.98 ± 0.01 |
| 6-fold | 3.25 ± 0.08 | 3.43 ± 0.54 | 0.98 ± 0.00 | 0.98 ± 0.01 |

RMSSD, root mean square of successive normal-to-normal sinus interval differences over the entire period of the experiment; $HR_{VR}$, heart rate (HR) variation ratio calculated by dividing the difference between the mean of HR values acquired during 60-s spontaneous and habitual breathing ($mHR_{BL}$) and that obtained during 15-s deep inspiration breath-holding into the $mHR_{BL}$ (expressed as a percentage); MAE, mean absolute error.

The values of MAE and Pearson's correlation coefficient were calculated between the apnea-hypopnea index predictive values and reference values measured with polysomnography.

Data are presented as the mean ± SD.

$P < 0.01$ for all Pearson's correlation coefficients.

Figure 3-7 shows the regression model that provided the smallest *k*-fold cross-validation error ($k = 2$, 4, and 6). The best-fitting curved surface (Figure 3-7, plaid surface) to the training data (Figure 3-7, solid circles) was derived from the rational function. The representation of the regression function is summarized in Table 3-7, along with the $R^2$ value. For the training set including the data of 100 individuals with an $AHI_{Refer}$ value (mean ± SD) of 22.6 ± 21.1 events/h, an absolute error (mean ± SD) of 3.17 ± 2.51 events/h and a Pearson's correlation coefficient of 0.98 ($P < 0.01$) were observed between $AHI_{Predi}$ and $AHI_{Refer}$. For the validation set that consisted of the data of the remaining 20 individuals with an $AHI_{Refer}$ value (mean ± SD) of 21.1 ± 19.9 events/h, an absolute error (mean ± SD) of 3.29 ± 2.64 events/h and a Pearson's correlation coefficient of 0.98 ($P < 0.01$) were exhibited between $AHI_{Predi}$ and $AHI_{Refer}$.

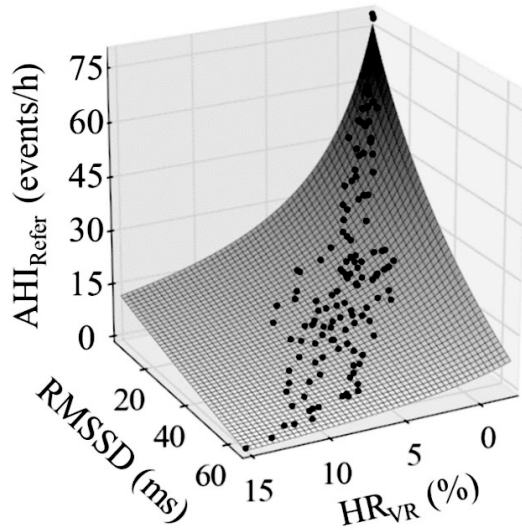



**Figure 3-7.** Regression model developed using the apnea-hypopnea index measured with polysomnography ($AHI_{Refer}$, dependent variable) and the two predictors (RMSSD and $HR_{VR}$). The best-fitting curved surface (plaid surface) to the training data (solid circles) was derived from the rational function.

**Table 3-7.** Parameters of the regression model using RMSSD and $HR_{VR}$ to predict apnea-hypopnea index

| Variable | | Regression function | $R^2$ |
|---|---|---|---|
| $y$ | $AHI_{Predi}$ (events/h) | | |
| $x_1$ | RMSSD (ms) | $y = \frac{89.16 - 0.91 \times x_1 - 2.88 \times x_2}{1 + 0.05 \times x_1 + 0.07 \times x_2}$ | 0.96 |
| $x_2$ | $HR_{VR}$ (%) | | |

RMSSD, root mean square of successive normal-to-normal sinus interval differences over the entire period of the experiment; $HR_{VR}$, heart rate (HR) variation ratio calculated by dividing the difference between the mean of HR values acquired during 60-s spontaneous and habitual breathing ($mHR_{BL}$) and that obtained during 15-s deep inspiration breath-holding into the $mHR_{BL}$ (expressed as a percentage); $AHI_{Predi}$, apnea-hypopnea index predictive value; $R^2$, coefficient of determination.

*Model III (Predictors: $RESP_{CV}$, RMSSD, and $HR_{VR}$)*

The statistical results of the regression analyses and 2-, 4-, and 6-fold cross-validation tests are summarized in Table 3-8.

The representation of the regression function, which provided the smallest *k*-fold cross-validation error ($k$ = 2, 4, and 6), is summarized in Table 3-9 along with the $R^2$ value. For the training set including the data of 100 individuals with an $AHI_{Refer}$ value (mean ± SD) of 22.0 ± 20.5 events/h, an absolute error (mean ± SD) of 2.65 ± 2.07 events/h and a Pearson's correlation coefficient of 0.98 ($P < 0.01$) were observed between $AHI_{Predi}$ and $AHI_{Refer}$. For the validation set that consisted of the data of the remaining 20 individuals with an $AHI_{Refer}$ value (mean ± SD) of 24.0 ± 22.6 events/h, an absolute error (mean ± SD) of 2.32 ± 1.93 events/h and a Pearson's correlation coefficient of 0.99 ($P < 0.01$) were exhibited between $AHI_{Predi}$ and $AHI_{Refer}$.

**Table 3-8.** Cross-validation statistics for apnea-hypopnea index predictive models developed using $RESP_{CV}$, RMSSD, and $HR_{VR}$

| Cross-validation | MAE (%) | | Pearson's correlation coefficient | |
|---|---|---|---|---|
| | Training set | Validation set | Training set | Validation set |
| 2-fold | 2.57 ± 0.19 | 2.76 ± 0.01 | 0.99 ± 0.00 | 0.98 ± 0.00 |
| 4-fold | 2.59 ± 0.18 | 2.74 ± 0.25 | 0.99 ± 0.00 | 0.99 ± 0.01 |
| 6-fold | 2.61 ± 0.07 | 2.74 ± 0.27 | 0.99 ± 0.00 | 0.99 ± 0.01 |

$RESP_{CV}$, coefficient of variation of respiration cycles acquired during the sleep-wake transition period; RMSSD, root mean square of successive normal-to-normal sinus interval differences over the entire period of the experiment; $HR_{VR}$, heart rate (HR) variation ratio calculated by dividing the difference between the mean of HR values acquired during 60-s spontaneous and habitual breathing ($mHR_{BL}$) and that obtained during 15-s deep inspiration breath-holding into the $mHR_{BL}$ (expressed as a percentage); MAE, mean absolute error.

The values of MAE and Pearson's correlation coefficient were calculated between the apnea-hypopnea index predictive values and reference values measured with polysomnography.

Data are presented as the mean ± SD.

$P < 0.01$ for all Pearson's correlation coefficients.

**Table 3-9.** Parameters of the regression model using $RESP_{CV}$, RMSSD, and $HR_{VR}$ to predict apnea-hypopnea index

| Variable | | Regression function | $R^2$ |
|---|---|---|---|
| $y$ | $AHI_{Predi}$ (events/h) | $y = 34.39 + 0.56 \times A - 2.44 \times x_1 + 0.01 \times A^2 + 0.05 \times {x_1}^2 - 5.03 \times 10^{-5} \times A^3 - 2.81 \times 10^{-4} \times {x_1}^3$ | 0.97 |
| $x_1$ | $RESP_{CV}$ (%) | | |
| $x_2$ | RMSSD (ms) | $\left(A = \frac{92.33 - 0.88 \times x_2 - 3.12 \times x_3}{1 + 0.06 \times x_2 + 0.06 \times x_3}\right)$ | |
| $x_3$ | $HR_{VR}$ (%) | | |

$RESP_{CV}$, coefficient of variation of respiration cycles acquired during the sleep-wake transition period; RMSSD, root mean square of successive normal-to-normal sinus interval differences over the entire period of the experiment; $HR_{VR}$, heart rate (HR) variation ratio calculated by dividing the difference between the mean of HR values acquired during 60-s spontaneous and habitual breathing ($mHR_{BL}$) and that obtained during 15-s deep inspiration breath-holding into the $mHR_{BL}$ (expressed as a percentage); $AHI_{Predi}$, apnea-hypopnea index predictive value; $R^2$, coefficient of determination.

### 3.3.3. Apnea-hypopnea index prediction model evaluation

Figure 3-8(a), (b), and (c) show the scatter plots of $AHI_{Predi}$ and $AHI_{Refer}$ obtained by applying Models I, II, and III, respectively, to the test set (Dataset IV) including the data of 30 individuals with an $AHI_{Refer}$ value (mean ± SD) of 23.0 ± 21.8 events/h. The values of the absolute error and Pearson's correlation coefficient obtained between $AHI_{Predi}$ and $AHI_{Refer}$ from each of the three models are summarized in Table 3-10. Figure 3-9(a), (b), and (c) show the Bland-Altman plots of the differences between $AHI_{Predi}$ and $AHI_{Refer}$ against the averages of $AHI_{Predi}$ and $AHI_{Refer}$ for Models I, II, and III, respectively. The mean of the differences (Figure 3-9, solid line) and the 95% limits of agreement (Figure 3-9, dashed lines), produced by each model, are summarized in Table 3-11. A comparison of the numerical values, described in Table 3-10 and Table 3-11, indicates that Model III has the greatest AHI predictability among the three models.

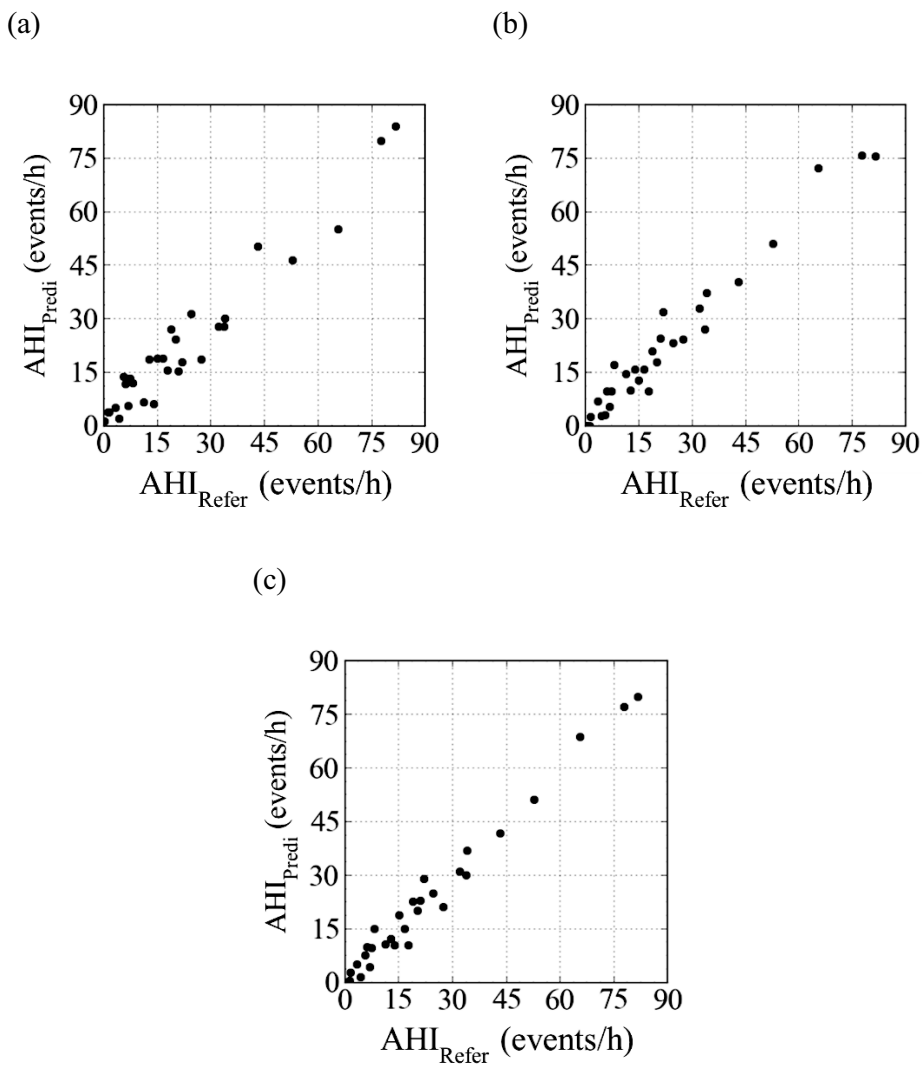



**Figure 3-8.** (a), (b), and (c) are scatter plots showing the relationship between the apnea-hypopnea index predictive values ($AHI_{Predi}$) provided by Models I, II, and III, respectively, and the apnea-hypopnea index reference values measured with polysomnography ($AHI_{Refer}$).

**Table 3-10.** Apnea-hypopnea index prediction performance assessed with absolute error and Pearson's correlation coefficient

| | Absolute error (events/h) | Pearson's correlation coefficient |
|---|---|---|
| Model I | 4.72 ± 3.86 | 0.97 |
| Model II | 3.27 ± 2.49 | 0.98 |
| Model III | 2.66 ± 1.97 | 0.99 |

The values of the absolute error and Pearson's correlation coefficient were calculated between the apnea-hypopnea index predictive values and reference values measured with polysomnography.

Absolute errors are presented as the mean ± SD.

$P < 0.01$ for all Pearson's correlation coefficients.

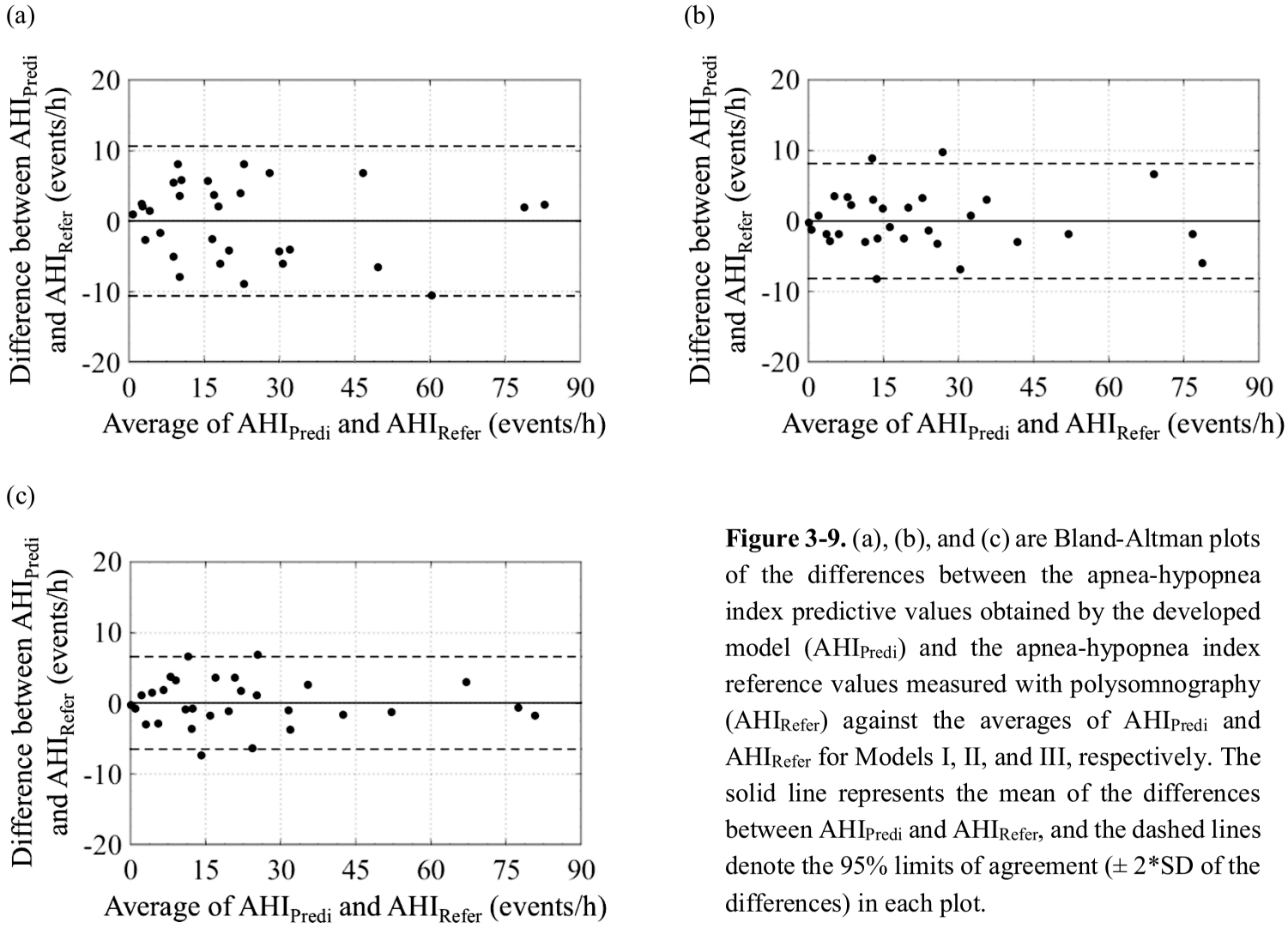



**Figure 3-9.** (a), (b), and (c) are Bland-Altman plots of the differences between the apnea-hypopnea index predictive values obtained by the developed model ($AHI_{Predi}$) and the apnea-hypopnea index reference values measured with polysomnography ($AHI_{Refer}$) against the averages of $AHI_{Predi}$ and $AHI_{Refer}$ for Models I, II, and III, respectively. The solid line represents the mean of the differences between $AHI_{Predi}$ and $AHI_{Refer}$, and the dashed lines denote the 95% limits of agreement (± 2*SD of the differences) in each plot.

**Table 3-11.** Apnea-hypopnea index prediction performance assessed by Bland-Altman analysis

| | Mean of differences (events/h) | 95% limits of agreement (events/h) |
|---|---|---|
| Model I | 0.07 | −10.53 - 10.67 |
| Model II | −0.02 | −8.16 - 8.11 |
| Model III | 0.04 | −6.50 - 6.58 |

The mean of differences and 95% limits of agreement (± 2*SD of the differences) values were calculated from the apnea-hypopnea index predictive values and reference values measured with polysomnography.

Table 3-12 summarizes the OSA diagnostic performance of Model III at AHI cut-off values of ≥ 5, 15, and 30 events/h. For the three different AHI cut-off values, an average sensitivity of 96.7%, an average specificity of 100.0%, an average PPV of 100.0%, an average NPV of 92.1%, an average accuracy of 97.8%, an average Cohen's kappa coefficient of 0.94 corresponding to almost perfect agreement, and an average ROC-AUC of 0.99 were reported. The OSA severity classification performance of Model III was also assessed. Table 3-13, a 4 × 4 contingency table, includes the number of subjects classified according to their OSA severity determined by $AHI_{Refer}$ (rows) and by $AHI_{Predi}$ (columns). In Table 3-13, the diagonal elements correspond to the number of subjects correctly categorized into their OSA severity in each group, while the off-diagonal elements indicate the number of subjects erroneously categorized. For the non-OSA group, all of the five non-OSA subjects were correctly classified as non-OSA subjects. For the mild and moderate OSA groups, one out of eight and one out of nine patients were misclassified, respectively. For the severe OSA group, all of the eight patients were correctly classified as severe OSA patients. When the correct classification rate (CCR) was derived from the percentage of the number of subjects correctly categorized into their respective OSA severity, Model III exhibited a CCR of 93.3%. No participants were misclassified beyond their contiguous severity groups; for instance, any OSA patient with mild severity was not classified as a severe OSA patient by Model III.

**Table 3-12.** Obstructive sleep apnea diagnostic performance

| | AHI cut-off (events/h) | | |
|---|---|---|---|
| | ≥ 5 | ≥ 15 | ≥ 30 |
| Sensitivity (%) | 96.0 | 94.1 | 100.0 |
| Specificity (%) | 100.0 | 100.0 | 100.0 |
| PPV (%) | 100.0 | 100.0 | 100.0 |
| NPV (%) | 83.3 | 92.9 | 100.0 |
| Accuracy (%) | 96.7 | 96.7 | 100.0 |
| Cohen's kappa coefficient | 0.89 | 0.93 | 1.00 |
| ROC-AUC | 0.99 | 0.98 | 1.00 |

AHI, apnea-hypopnea index; PPV, positive predictive value; NPV, negative predictive value; ROC-AUC, area under the receiver operating characteristics curve.

Cohen's kappa coefficients ranging from 0.81 to 1.00 indicate almost perfect agreement.

**Table 3-13.** Obstructive sleep apnea severity classification performance

| | | OSA severity determined by Model III | | | | Total |
|---|---|---|---|---|---|---|
| | | Non-OSA | Mild | Moderate | Severe | |
| OSA severity assessed by PSG | Non-OSA | 5 | 0 | 0 | 0 | 5 |
| | Mild | 1 | 7 | 0 | 0 | 8 |
| | Moderate | 0 | 1 | 8 | 0 | 9 |
| | Severe | 0 | 0 | 0 | 8 | 8 |
| Total | | 6 | 8 | 8 | 8 | 30 |

OSA, obstructive sleep apnea; PSG, polysomnography.

OSA severity was categorized according to an apnea-hypopnea index (AHI) value as "Non-OSA" (AHI < 5 events/h), "Mild" (5 ≤ AHI < 15 events/h), "Moderate" (15 ≤ AHI < 30 events/h), and "Severe" (AHI ≥ 30 events/h).

## 3.4. Discussion

New reliable predictors of the AHI were suggested based on the assessment of the autonomic influence on respiration and the HR. One of these AHI predictors is $RESP_{CV}$; a smaller $RESP_{CV}$ is related to a higher AHI, which might result from less irregular respiration cycles during the sleep-wake transition period in more severe OSA patients because of their unresponsive ANS. Another AHI predictor is RMSSD; a smaller RMSSD is associated with a higher AHI, which would be caused by the greater attenuation of the waking vagal tone in patients with more severe OSA. Lastly, $HR_{VR}$ is another AHI predictor; a smaller $HR_{VR}$ is related to a higher AHI, which might be produced by the less effective vagal response that contributes to the smaller decrease in HR during DIBH compared to spontaneous and habitual breathing in more severe OSA patients.

The AHI prediction model developed using RMSSD and $HR_{VR}$ (Model II) exhibited better predictive ability than that established using $RESP_{CV}$ (Model I). This result indicates that although autonomic dysfunction in OSA patients is expressed by both sympathetic and parasympathetic abnormalities, the assessment of vagal downregulation is more useful in predicting the AHI. This is in agreement with the previous finding of Hilton *et al*. The authors observed that the waking vagal tone estimated from the HF component of the HRV power spectrum was reduced in patients with mild-to-moderate OSA compared to healthy controls with corresponding age, gender, BMI, and BP.

However, the daytime sympathetic activity, assessed from urine catecholamines, did not differ between the groups [95]. The characteristics of the HR, which directly reflects autonomic imbalance because the depolarization rate of the sinoatrial node is mainly determined by ANS activity, could also contribute to the ability of RMSSD and $HR_{VR}$ to predict the AHI [98].

Several studies have reported on the relationship between the AHI and electrocardiographic parameters acquired during wakefulness. Maeder *et al*. explored 31 mild-to-moderate OSA syndrome (OSAS) patients and 32 severe OSAS patients. They observed a Pearson's correlation coefficient of −0.32 ($P = 0.01$) between the natural-log-transformed AHI values and the natural-log-transformed HR recovery values, measured during the first minute after exercise (HRR-1) [99]. Nanas *et al*. reported a Pearson's correlation coefficient of −0.50 ($P < 0.02$) between the AHI and HRR-1 obtained from 21 moderate-to-severe OSA patients and 10 healthy subjects matched for age and BMI [100]. Çiçek *et al*. acquired the 24-h HR, HRR-1, QT-corrected interval (QTc), and P-wave dispersion (Pd) from 26 non-OSAS subjects and 20 mild OSAS, 20 moderate OSAS, and 20 severe OSAS patients. Their study showed that the mean HR during 24 h of wakefulness and sleep was correlated significantly with the AHI (Spearman's rho = 0.037, $P = 0.0002$), HRR-1 was negatively correlated with the AHI (Spearman's rho = −0.32, $P = 0.0001$), QTc was positively correlated with the AHI (Spearman's rho = 0.44, $P = 0.03$),

and Pd was positively correlated with the AHI (Spearman's rho = 0.389, $P$ = 0.001) [98]. Although the aforementioned studies revealed significant relationships between the AHI and the 24-h HR, HRR-1, QTc, and Pd values, the lack of AHI explanation power of these electrocardiographic parameters limited their applicability as effective predictors of the AHI. The two new electrocardiographic parameters proposed in this study exhibited stronger correlations with the AHI (Spearman's rho absolute values exceeding 0.9, $P$ < 0.01). Therefore, their utilization facilitated the development of a reliable AHI prediction model.

Because there is no study to predict the AHI, a relative evaluation of the AHI prediction performance of Model III could not be performed. Instead, Model III could be compared with previously proposed screening tools with respect to its OSA diagnostic performance. In Table 3-14, the sensitivities and specificities of OSA diagnoses obtained with different screening tools are summarized according to the AHI cut-off values. For each group indicated in Table 3-14, the screening tools displayed in the first and second rows are the tools that exhibited the best OSA diagnostic sensitivity and specificity, respectively. The third row shows the performance of Model III. It is notable that Model III is the only tool that provided consistently good performance in identifying OSA at multiple AHI cut-off values. As shown in Table 3-14, a sensitivity ranging from 94 to 100% confirms that Model III could be effective for the early identification of OSA, thus decreasing the healthcare

costs associated with the treatment of comorbidities. Additionally, the specificities, which range from 90 to 100%, demonstrate that Model III may be helpful to avoid unnecessary testing, which enables the efficient utilization of sleep clinic resources.

**Table 3-14.** Comparison of the performance of obstructive sleep apnea prediction methods

| Tool | Subject | Sensitivity (%) | Specificity (%) |
|---|---|---|---|
| Wisconsin questionnaire [46] | 38 AHI ≥ 5<br>112 AHI < 5 | 95 | 64 |
| Berlin questionnaire [47] | 62 AHI > 5<br>42 AHI < 5 | 86 | 95 |
| Model III | 25 AHI ≥ 5<br>5 AHI < 5 | 96 | 100 |
| Self-developed clinical prediction model [39] | 104 AHI ≥ 10<br>46 AHI < 10 | 99 | 80 |
| Craniofacial photo-graphic analysis [101] | 114 AHI ≥ 10<br>66 AHI > 10 | 48 | 92 |
| Model III | 20 AHI ≥ 10<br>10 AHI < 10 | 100 | 90 |
| Features from tracheal breath sound [52] | 22 AHI > 15<br>30 AHI < 15 | 95 | 81 |
| Berlin questionnaire [40] | 70 AHI ≥ 15<br>30 AHI < 15 | 54 | 97 |
| Model III | 17 AHI ≥ 15<br>13 AHI < 15 | 94 | 100 |
| STOP-Bang questionnaire [22] | 39 AHI > 30<br>138 AHI ≤ 30 | 100 | 37 |
| Negative expiratory pressure test [51] | 24 AHI ≥ 30<br>24 AHI < 5 | 96 | 96 |
| Model III | 8 AHI ≥ 30<br>22 AHI < 30 | 100 | 100 |

AHI, apnea-hypopnea index.

To the best of my knowledge, the present study is the only study that has obtained AHI predictive values without overnight recording, and has verified its prediction ability for multi-categorized OSA severity. It should be noted that all the subjects misclassified their OSA severity by Model III were found in a "gray zone" where AHI values around a discrete boundary between contiguous severity groups were included. The use of AHI predictive values instead of dichotomously classified OSA diagnostic conjecture may be useful to provide corroborating evidence in clinical decision-making associated with the need and urgency for formal diagnosis and treatment of OSA. In addition to the ability of the proposed method to predict an AHI value, its validity is unquestionable because it does not rely on subjective reports, unlike existing questionnaires for OSA screening. A systemic review of these questionnaires has shown their unreliability through their varied performance across different studies [48]. For instance, the screening of severe OSA (AHI $\geq$ 30 events/h) patients using the Berlin questionnaire was validated with a sensitivity of 87% by Chung *et al*. [23] but with a sensitivity of 17% by Netzer *et al*. [40]. Compared to existing methods that use anatomico-functional features as OSA predictors, the proposed method exhibits satisfactory efficiency, as it involves a faster and simpler procedure, and improved comfortability, as the suggested predictors can be acquired from unconstrained physiological signal measurement.

This study has some limitations. The first is related to its generalizability.

The AHI prediction models proposed in this study are not applicable to OSA patients with cardiovascular complications. In future work, I will analyze the characteristics in such patients' cardiac response, affected or not affected by medications for cardiovascular diseases, to breath-holding experiments. The second limitation is associated with reproducibility. It is necessary to explore the effects of changes in the time interval between the breath-holding experiment and sleep and in the duration of the experiment on the reliability of the proposed AHI predictors. The third limitation is related to the validation strategy. Further validation of the proposed method using external datasets, especially those obtained using different monitoring systems of physiological signals, may contribute to improving the applicability of this study.

# Chapter 4. Discussion

The aim of this study was to determine reliable predictors of SE and AHI. Based on the bi-directional relationships between sleep and ANS activity and between ANS activity and cardiorespiratory signal, it was possible to hypothesize that cardiorespiratory features obtained during the sleep-onset period could be effective in predicting SE and AHI.

The SE prediction model, developed using LF/HF and $PIFR_{avg}$, exhibited better performance compared to existing tools proposed as alternatives to PSG for SE estimation. The SE predictability of LF/HF and $PIFR_{avg}$ can be explained by the effect of pre-sleep sympathetic activation on sleep.

Unlike previously proposed tools for OSA screening, the AHI prediction model established using $RESP_{CV}$, RMSSD, and $HR_{VR}$ provided consistently good performance in diagnosing OSA at multiple AHI cut-off values. The effectiveness of the suggested AHI predictors can be explained by the impaired autonomic function in OSA patients.

This study has the potential to be utilized for home-based, long-term monitoring of SE and AHI, and to support effective decision-making on the implementation of SE improvement strategies and on the need for formal diagnosis and treatment of OSA.

It is required to assess the effectiveness of each suggested predictor according to its acquisition time, which can be useful in providing information about an optimal time for cardiorespiratory signal measurement.

There are many commercialized devices used for unconstrained monitoring of cardiorespiratory signals. The methodology devised in this study will be applied to these devices to ensure its reliability and expand its applicability in future work.

# Chapter 5. Conclusions

In this study, new predictors of SE and AHI have been suggested. The HRV and breathing parameters, acquired during a 5-min awake resting period, were effective in predicting the SE. The irregularity of respiration cycles obtained during a 150-s sleep-wake transition period, and the HR changes observed during 60-s spontaneous and habitual breathing and consecutive 15-s DIBH were useful for the reliable prediction of the AHI in OSA patients.

Compared with the standard method used to obtain the SE and AHI, the first novelty of the proposed method is the absence of a requirement for overnight recording. In this regard, the proposed method could be useful in terms of time and resource efficiency and the ability to provide opportunities to improve sleep. The second novelty is that the suggested predictors can be acquired unobtrusively, thus improving the potential applicability of this study to long-term SE and AHI monitoring in out-of-sleep laboratory environments.

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# Abstract in Korean

이 연구에서는 입면 구간에서 무구속적인 방식으로 측정된 심폐신호를 사용해 수면 변인들을 예측할 수 있는 새로운 방법을 개발하였다.

첫번째로 예측한 수면 변인은 수면 효율이다. 수면 효율은 잠자리에 누워있는 시간과 실제 수면을 취한 시간 사이의 비율로 계산되며 수면의 질을 객관적으로 평가하기 위해 가장 널리 사용되는 지표이다. 수면 효율의 예측인자로 고려된 것은 수면 전 관찰되는 자율신경계의 상태이다. 이를 비침습, 무구속 방식으로 평가하기 위해 피험자에게 필름 타입의 압전센서가 설치된 침대 매트리스 위에 깨어 있되 안정된 상태로 5분 간 누워있도록 지시한 후, 그동안 획득한 심폐신호로부터 심박변이도 및 호흡 특성을 추출하였다. 교감신경의 활성과 관련된 심박변이도 및 호흡 특성을 이용해 추정된 수면 효율은 실제 수면 효율과 평균적으로 약 2.2%의 절대 오차를 보였다.

두번째로 예측한 수면 변인은 폐쇄성 수면 무호흡증 환자의 무호흡-저호흡 지수이다. 무호흡-저호흡 지수는 수면 시간 당 발생한 무호흡과 저호흡 횟수로 계산되며 폐쇄성 수면 무호흡의 심각도를 판단하기 위해 가장 널리 사용되는 지표이다. 또한 폐쇄성 수면 무호흡의 심혈관계 합병증 위험도와 유의미한 관계를 보이는 지표로서 무호흡-저호흡 지수는 임상적으로 중요한 의미를 갖는다. 무호흡-저호흡 지수의 예측인자로 고려된 것은 들숨 상태에서 일정 시간 동안 호흡을 멈추는 과정을 통해 나타나는 심박 변화와 입면 기에 관찰되는 호흡 주기의

불규칙성이다. 이러한 예측인자들은 각각 75초, 150초 동안 필름 타입의 압전센서가 설치된 침대 매트리스 위에 누워 있는 피험자에게서 무구속적으로 획득한 심폐신호로부터 추출되었다. 해당 예측인자들을 사용해 추정된 무호흡-저호흡 지수는 실제 무호흡-저호흡 지수와 평균적으로 약 2.7회/시간의 절대 오차를 보였다.

수면 변인들을 얻기 위해 표준적으로 사용되는 방법과 비교해 이 연구에서 개발된 방법이 갖는 첫번째 차별성은 생체 신호의 밤샘 기록 없이 입면 구간에서 수 분 동안 획득한 생체 신호를 사용해 수면 변인을 예측한다는 것이다. 이는 시간 및 자원 이용 효율성을 높이고 수면 변인의 예측 값을 근거로 하여 수면을 향상시킬 수 있는 기회를 제공한다는 점에서 활용 가치를 갖는다. 두번째 차별성은 제안된 수면 변인의 예측인자들을 무구속적으로 측정한 심폐신호로부터 추출 가능하다는 점이다. 이로부터 기대할 수 있는 효과는 예측인자의 획득을 위한 생체 신호 측정 시 피험자가 느낄 수 있는 신체적 불편함을 최소화 함으로써 개발된 방법이 가정환경에서 장기간 활용될 수 있도록 하는 것이다.

**주요어:** 수면 효율, 무호흡-저호흡 지수, 폐쇄성 수면 무호흡, 입면 구간, 심폐신호, 압전센서

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