ELSEVIER

Sleep Medicine 4 (2003) 537–542

SLEEP MEDICINE

www.elsevier.com/locate/sleep

Original article

Clinical significance of pulse rate rise during sleep as a screening marker for the assessment of sleep fragmentation in sleep-disordered breathing

Hiroyoshi Adachi[a,b,*], Akira Mikami[a,c], Takayuki Kumano-go[a,b], Nakamori Suganuma[a,b], Hideyuki Matsumoto[a,b], Yoshihisa Shigedo[a], Yoshiro Sugita[b], Masatoshi Takeda[a]

[a]*Department of Post Genomics and Diseases, Division of Psychiatry and Behavioral Proteomics, Osaka University Graduate School of Medicine, D-3, 2-2, Yamadaoka, Suita, Osaka 565-0871, Japan*

[b]*Department of Medical Science III, Osaka University School of Health Sport Sciences, Toyonaka, Osaka, Japan*

[c]*Osaka Prefectural Mental Health Center, Osaka, Japan*

Received 18 March 2003; received in revised form 20 May 2003; accepted 12 June 2003

Abstract

Objective: To assess the clinical utility of the frequencies of transient increases of pulse rate, non-invasively measured with a pulseoximeter, as an indirect indication of the degree of cortical arousal, measured conventionally on an electroencephalogram (EEG), in obstructive sleep apnea–hypopnea syndrome (OSAHS) patients.

Patients and Methods: Thirty-three consecutive patients referred with suspected OSAHS were studied. Polysomnography (PSG) with determination of esophageal pressure (Pes) and pulseoximetry was monitored to identify breathing-related EEG arousal (B-Ar) associated with apnea, hypopnea or respiratory effort and the frequencies of pulse rate increases. We also assessed the association of B-ArI (defined as the number of B-Ar per hour) with the pulse rate rise index (PRRI)-X ($X = 4–10$) (defined as the number of pulse rate increases per hour). In addition, the sensitivity and specificity of PRRI for the assessment of a B-ArI cutoff point of 30 were calculated.

Results: The sensitivity and specificity of pulseoximetry for different thresholds of PRRI-X ($X = 4–10$) demonstrated that the greatest diagnostic accuracy for detecting frequent arousal (B-ArI ≥ 30) occurs at a cutoff point of 40 PRRI-6 with a sensitivity of 0.88 and specificity of 0.86. This point shows a significant area under the curve of 0.84. In addition, a statistically significant correlation between PRRI-6 and B-ArI ($r = 0.68$, $P < 0.0001$) was observed.

Conclusions: The transient increases in pulse rate measured by pulseoximetry during sleep may be a useful clinical marker for predicting the degree of arousal in OSAHS patients, and may, in addition, prevent cases with frequent respiratory effort related arousals from being overlooked. However, further studies are required to improve the confidence level of the PRRI and to investigate the causes of overestimation of EEG arousals.

Keywords: Pulse rate; Pulseoximeter; Sleep apnea–hypopnea; Arousal; Screening; Polysomnography

1. Introduction

Obstructive sleep apnea–hypopnea syndrome (OSAHS) is characterized by repetitive episodes of upper airway narrowing and breathing pauses. OSAHS is terminated by arousal from sleep and is frequently accompanied by a transient increase in inspiratory effort. Such sleep fragmentation has been implicated in daytime sleepiness, poor sleep quality and impairment of psychomotor performance [1,2]. Excessive daytime sleepiness (EDS) is a major common symptom in OSAHS patients leading to referral to a sleep laboratory.

Polysomnography (PSG) is widely accepted as the gold standard for the diagnosis of OSAHS, and the apnea–hypopnea index (AHI) has generally been used for evaluation of the severity of OSAHS. A disadvantage of using the AHI as a measure of sleep disruption is that this method may not detect episodes of airway narrowing that fail to reduce the airflow signal but increase the inspiratory effort sufficiently to result in an arousal [3]. For these cases,

* Corresponding author. Address: Course of Advanced Medicine, Department of Post-Genomics and Diseases, Division of Psychiatry and Behavioral Proteomics, Osaka University Graduate School of Medicine, D-3, 2-2, Yamadaoka, Suita, Osaka 565-0871, Japan. Tel.: +81-6-6879-3055; fax: +81-6-6879-3059.

E-mail address: hadachi@psy.med.osaka-u.ac.jp (H. Adachi).

1389-9457/$ - see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/j.sleep.2003.06.003

esophageal pressure (Pes) manometry demonstrates progressive negative pressures followed by frequent arousals. We have reported that AHI is inadequate for the detection of breathing-related arousals, especially in cases with low AHI [4]. Measuring cortical arousals by logging increases in frequency on electroencephalogram (EEG) and electromyogram (EMG) has been the standard technique for quantifying the number of arousals during sleep and for providing an index of sleep fragmentation. The number of arousals is, in fact, a useful marker of sleep quality. However, PSG is relatively expensive and time consuming, and its availability is limited in many areas.

Previous reports have suggested that home oximetry is useful for detecting obstructive sleep apnea (OSA), but that it may show discrepant results [5–14]. Home oximetry involves less equipment and labour than does PSG. However, few studies have evaluated the utility of changes in pulse rate during sleep, as measured by pulseoximetry, for predicting whether significant sleep fragmentation is present in OSAHS patients. The pathophysiology of OSAHS as a whole is underestimated if only desaturation is used during screening to estimate the severity of OSAHS. Therefore, an automated or other well-defined method of detecting sleep fragmentation is warranted as a screening tool. The aim of this study is to assess the clinical value of the frequencies of transient increases of pulse rate, measured by pulseoximetry, as an indirect marker of the degree of cortical arousal measured by EEG.

2. Materials and methods

2.1. Subjects

The study group consisted of 33 consecutive adult patients referred to our sleep-disorders unit for suspected OSAHS due to snoring, nocturnal choking and awakenings, apneic events or all three reported by a bedmate, poor quality of sleep, and/or daytime hypersomnolence. We studied 29 men and 4 women, ages 25–69 years (mean, 49.1 ± 13.1). All patients were examined by electrocardiogram and were found to be free of unstable cardiovascularity and of any history of cardiopulmonary disease. Two cases with hypertension were stable clinically and in sinus rhythm. Since the purpose of this study was to evaluate breathing-related EEG arousals, cases with periodic limb movement disorder, which frequently involves sleep fragmentation, were excluded.

2.2. Measurements

PSG included the following channels: central and occipital EEG (C3/A2, C4/A1, O2/A1, O1/A2 of the international 10–20 electrode placement system), electrooculogram, electrocardiogram (modified V2), chin electromyogram, oronasal airflow by thermistor, snoring, arterial oxygen saturation, body position, and bilateral anterior tibialis electromyogram. Thoracic and abdominal movements were monitored with thoracic and abdominal piezoelectric strain gauges. The respiratory effort was monitored by means of Pes measurement. The esophageal catheter was placed transnasally and calibrated according to the technique described by Baydur et al. [15]. All signals were recorded continuously on paper through a 14-channel polygraph (Nihonkoden, Tokyo, Japan). Pulse rate change was measured by a finger pulseoximeter (Minolta, Pulsox-M24). This pulseoximeter samples a new pulse rate value every pulse rate by averaging the new pulse rate with the most recent consecutive eight pulse rates. The pulseoximetry data were analysed with the software program DS-M version 3.0 (Minolta Associates, Inc., Japan), which was designed for use with the Pulsox-M24. The DS-M program measures the consecutive peak and valley points of pulse rates and counts the number of pulse rate increases $\geq 4-10$ beats. Sleep stages were identified in 30-s epochs according to the guidelines of Rechtschaffen and Kales [16]. Apnea was defined as a complete cessation of airflow for more than 10 s. Hypopnea was defined as either a decrease ($>50\%$) in amplitude from the baseline of airflow, or a clear decrease ($<50\%$) in amplitude followed by either oxygen desaturation ($>3\%$) or an arousal [17]. Arousals were defined in accordance with a preliminary report from the American Sleep Disorders Association Atlas Task Force [18].

The AHI was calculated as the average number of episodes of apnea and hypopnea per hour of sleep. We also defined breathing-related EEG arousal (B-Ar) as EEG arousal associated with apnea, hypopnea or respiratory effort related to increases in Pes and the B-Ar index (B-ArI) as the number of B-Ar per hour. Respiratory effort related arousal (RERA) was defined as an increase in respiratory effort for ≥ 10 s leading to an arousal from sleep that did not fulfil the criteria for hypopnea or apnea. The RERA index (RERAI) was defined as the number of RERAs per hour of sleep. We calculated the frequency of changes in the pulse rate and defined the pulse rate rise index (PRRI)-X ($X = 4-10$) as the number of pulse rate increases per hour. For example, PRRI-4 represents the number of increases by more than four beats per hour during sleep. In this study, a diagnosis of OSAHS was made if PSG showed AHI ≥ 5 or B-ArI ≥ 10.

2.3. Analysis

The subjects were divided into two groups according to the B-ArI value in order to determine the ability of pulseoximetry to differentiate between mild and more severe disease. A cutoff point of 30 for the B-ArI was used to evaluate the severity of breathing-related EEG arousal; in this study a B-ArI ≥ 30 was considered to represent frequent breathing-related EEG arousals (the frequent arousal group), and cases with a B-ArI < 30 were defined as the milder arousal group. Receiver

Table 1
Summary characteristics of the study population

	Age (years)	Male/female	AHI	RERAI	B-ArI
Overall ($n = 31$)	48.2 ± 12.9	28/3	31.8 ± 28.9	9.6 ± 8.5	38.7 ± 23.9
B-ArI ≤ 30 ($n = 14$)	44.4 ± 14.2	12/2	12.0 ± 9.2	9.9 ± 5.6	19.5 ± 6.1
B-ArI > 30 ($n = 17$)	51.4 ± 11.2	16/1	48.1 ± 29.5	9.3 ± 10.4	54.5 ± 21.2
AHI ≤ 30 ($n = 18$)	49.0 ± 13.7	15/3	10.7 ± 6.4	13.7 ± 8.0	23.4 ± 8.6
AHI > 30 ($n = 13$)	47.2 ± 12.3	13/0	61.1 ± 20.8	3.8 ± 5.3	59.8 ± 22.0

Data are mean ± SD. B-ArI, breathing-related EEG arousal index; AHI, apnea–hypopnea index; RERAI, respiratory effort related arousal index.

operating characteristic (ROC) analysis was used to determine whether a certain PRRI might be used to discriminate patients with frequent breathing-related EEG arousal (B-ArI ≥ 30) from those without it. The sensitivity and specificity of pulseoximeter monitoring for the different thresholds for PRRI were also calculated. In addition, the Pearson's correlation coefficient between PRRI and B-ArI was calculated to assess their relationship. Data are expressed as the mean(±SD) unless otherwise stated. Statistical significance was accepted for $P \leq 0.05$.

3. Results

Of the 33 patients studied, pulseoximetry and PSG recordings were completed for all overnight sleep studies. However, two subjects were identified as having periodic limb movement disorder and were excluded from further analysis. Table 1 summarizes the demographic and polysomnographic variables of the 31 patients studied. Two cases were normal, with an AHI < 5 and a B-ArI < 10. The mean AHI and B-ArI for the entire cohort were 31.8(±28.9) and 38.7(±23.9), respectively. Seventeen subjects showed frequent arousals (B-ArI ≥ 30), and 14 showed a milder sleep fragmentation with a B-ArI < 30. The mean AHI and B-ArI for the frequent arousal group were 48.1(±29.5) and 54.5(±21.2), and those for the milder arousal group were 12.0(±9.2) and 19.5(±6.1), respectively. The mean B-ArI and AHI were significantly different for the two groups ($P < 0.01$).

The sensitivity and specificity of pulseoximetry at different PRRI thresholds were calculated. The validity indices of the optimal cutoff points for each PRRI are shown in Table 2. In order to further assess the efficacy of the PRRI as a potential tool for identifying sleep fragmentation, the ROC curve for a B-ArI cutoff point of 30 was obtained and the area under the curve (AUC) was calculated. The greatest diagnostic accuracy for detection in the frequent arousal group (B-ArI ≥ 30) occurs at a cutoff point of 40 PRRI-6, with a sensitivity of 0.88, a specificity of 0.86, and a significant AUC of 0.84. Fig. 1 shows the ROC curve for PRRI-6. The specificity declined for PRRI values of less than PRRI-5, so that the subjects could be clearly identified with the sensitivity well preserved. However, in these cases, the false positive rate was high.

Scatter diagrams (Fig. 2) display the relationship between PRRI-6 and the B-ArI for the entire study population. A statistically significant correlation was observed between the two parameters ($r = 0.68$, $P < 0.0001$). However, the B-ArI and PRRI in one patient were not always similar to those in another patient, and the findings also suggest that PRRI tends to overestimate the frequency of sleep fragmentation in terms of cortical EEG arousals.

4. Discussion

In the present study, we have assessed the potential usefulness of pulseoximetry as a screening test for sleep fragmentation in a population of patients suspected of having OSAHS. A significant correlation was observed between pulse rate change and breathing-related arousal. The PRRI-6 cutoff point of 40 was chosen as the best compromise between high sensitivity and relatively well-preserved specificity for detecting cases with a B-ArI ≥ 30. Our results indicate that PRRI is a sensitive marker of the frequency of arousals in OSAHS patients.

OSAHS is characterized by recurrent episodes of partial or complete upper airway obstruction during sleep [3], which leads to an increase in Pes manifested as respiratory efforts, arousals (sleep fragmentation) and oxygen desaturation. The AHI remains the primary tool for assessing the severity of OSAHS, but may fail to reveal the severity of negative Pes, which is an important aspect of

Table 2
Sensitivity and specificity of PRRI, and areas under the ROC curve for the various PRRI levels, referred to B-ArI cutoff point of 20

Frequencies of pulse rate rise	Cutoff point	Sensitivity	Specificity	AUC
PRRI-4	50	0.94	0.64	0.84
PRRI-5	40	0.88	0.64	0.85
PRRI-6	40	0.88	0.86	0.84
PRRI-7	30	0.88	0.71	0.81
PRRI-8	30	0.82	0.78	0.82
PRRI-9	20	0.88	0.71	0.81
PRRI-10	20	0.82	0.79	0.80

PRRI, pulse rate rise index; ROC curve, receiver-operating characteristic curve. PRRI-X : $X = 4–10$; AUC, areas under the ROC curve.

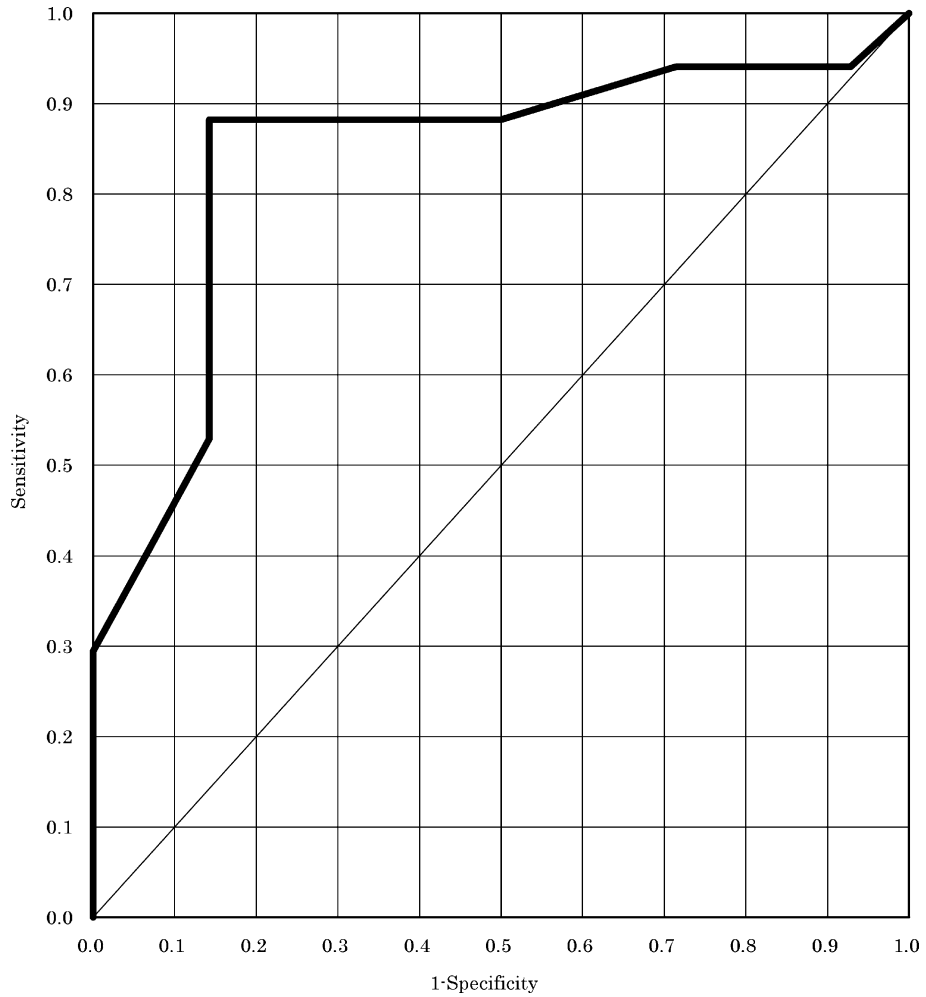

Fig. 1. Receiver-operating characteristic curve obtained with PRRI-6 for the identification of frequent breathing-related EEG arousal (B-ArI ≥ 30). The area under the curve is 0.84, indicating a high sensitivity and a well preserved specificity (0.88 and 0.86, respectively) for the assessment of breathing-related EEG arousal frequency by PRRI-6.

the pathophysiology of OSAHS [19]. It is impossible to assess oxygen desaturation and arousal separately with the AHI because apnea–hypopnea is defined as the result of the simultaneous assessment of these two different factors [17]. The correlation between the AHI and B-ArI has been suggested to be poor in OSAHS cases with a lower AHI [4]. Therefore, oxygen desaturation or apnea–hypopnea may occur separately from arousal in mild or moderate OSAHS patients, even though they are diagnosed by the AHI with the same severity of OSAHS. In particular, cases with frequent RERAs display a milder degree of upper airway obstruction, and no events have been defined as criteria for apnea or hypopnea. Nevertheless, arousals frequently occur due to the increased respiratory effort.

Many studies have assessed the usefulness of pulse-oximetry during sleep for detecting OSAHS [5–14]. Most of these studies have used only oxygen saturation monitoring to access OSAHS, while pulse rate change has not been examined. Since daytime hypersomnolence might be the direct result of recurrent arousals during sleep, estimating the degree of sleep fragmentation is an important part of a respiratory sleep study. In addition, the influence of the entire pathophysiology of OSAHS may be under-estimated if only desaturation is used to estimate the severity

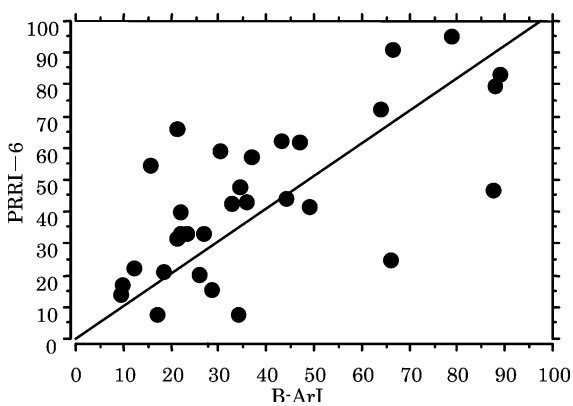

Fig. 2. Comparison of B-ArI vs PRRI-6 by means of a scatter plot with a regression line. A statistically significant correlation ($r = 0.68$, $P < 0.0001$) was obtained.

of OSAHS at screening. Thus, there is a practical necessity for measuring the degree of sleep fragmentation in OSAHS. The advantages of using PRRI for screening of OSAHS include the simplicity and minimal technical intervention in patient preparation and recording. The frequency of pulse rate changes may be useful for predicting the degree of arousal because arousal from sleep is associated with transient sympathetic nerve activation [20–25].

Several limitations to the present study and shortcomings in the use of PRRI exist. Our results suggest that the PRRI allows for confident identification of moderate and severe sleep fragmentation in OSAHS, but our initial study indicated that the PRRI is inadequate for discrimination of milder cases in terms of sleep fragmentation. Furthermore, the availability of PSG is limited in our sleep-disorders unit, so we could not evaluate normal cases adequately. Therefore, our results were not able to differentiate milder cases, such as a B-ArI < 30, from normal cases with a AHI < 5 and a B-ArI < 10. Although only two normal cases were identified in our study, detecting milder cases accurately with certain exclusion of the normal variants using PRRI is difficult. This suggests that it is likely to be impossible to detect cases with milder sleep fragmentation, which is consistent with the results of previous studies investigating the utility of oximetry for evaluation of the AHI in OSAHS patients. Those studies reported that oximetry screening detected most patients with severe or moderate OSAHS but was not useful for milder cases [26]. However, despite this limitation, we believe that the analysis of pulse rate change has great value as a screening tool because it is able to detect cases with frequent sleep fragmentation that show only a lower desaturation level with oximetry. To examine these aspects, further investigations with a larger sample size, including more normal variants, are required.

The other clinical limitation of our results is that the PRRI tends to overestimate the degree of EEG arousals in some cases, preventing the attainment of high specificity. For this reason, several factors must be considered. At first, the PRRI is assumed to represent not only EEG 'cortical' arousal according to the ASDA criteria, but also some degree of sympathetic nerve activation that does not necessarily correspond to EEG arousal. Our study examined ASDA EEG arousal only. Many studies have focused on other types of arousal associated with heart rate changes, such as the so-called 'subcortical arousal' without EEG correlate, delta bursts, K-bursts, phases of transitory activation (PAT), and cyclic alternating pattern (CAP) [27–29]. In addition, the variability of RR during REM sleep must be considered because of its association with augmented sympathetic nerve activation relative to non-REM sleep [30,31]. Further, periodic fluctuations in respiration, such as Cheyne Stokes respiration, are known to be associated with oscillations in heart rate and blood pressure, which may be related to periodic changes in sympathetic and vagal tone. Therefore, in patients with congestive heart failure, for example, it is unknown if the PRRI could extract the arousals accurately. Thus, further studies are needed to evaluate the relationships between PRRI and these factors.

References

[1] Martin SE, Engleman HM, Deary IJ, et al. The effect of sleep fragmentation on daytime function. Am J Respir Crit Care Med 1996; 153:1328–32.

[2] Martin SE, Wraith PK, Deary IJ, et al. The effect of nonvisible sleep fragmentation on daytime function. Am J Respir Crit Care Med 1997; 155:1596–601.

[3] Guilleminault C, Stoohs R, Clerk A, et al. A cause of excessive daytime sleepiness. The upper airway resistance syndrome. Chest 1993;104:781–7.

[4] Kumano-go T, Mikami A, Suganuma N, et al. Three components of obstructive sleep apnea/hypopnea syndrome. Psychiatry Clin Neurosci 2003;57:199–205.

[5] Bonsignore G, Marrone O, Macalso C, et al. Validation of oximetry as a screening test for obstructive sleep apnoea syndrome. Eur Respir J 1990;10(Suppl):542–544s.

[6] Williams AJ, Yu G, Santiago S, et al. Screening for sleep apnea using pulse oximetry and a clinical score. Chest 1991;100:631–5.

[7] Cooper BG, Veale D, Griffiths CJ, et al. Value of nocturnal oxygen saturation as a screening test for sleep apnoea. Thorax 1991;46: 586–8.

[8] Yamashiro Y, Kryger MH. Nocturnal oximetry: is it a screening tool for sleep disorders? Sleep 1995;18(3):167–71.

[9] Gyulay S, Olson LG, Hensley MJ, et al. A comparison of clinical assessment and home oximetry in the diagnosis of obstructive sleep apnea. Am Rev Respir Dis 1993;147:50–3.

[10] Series F, Marc I, Cormier Y, et al. Utility of nocturnal home oximetry for case finding in patients with suspected sleep apnea hypopnea syndrome. Ann Intern Med 1993;119:449–53.

[11] Pepin JL, Levy P, Lepaulle B, et al. Does oximetry contribute to the detection of apneic events? Mathematical processing of the SaO2 signal. Chest 1991;99:1151–7.

[12] Douglas NJ, Thomas S, Jan MA. Clinical value of polysomnography. Lancet 1992;339:347–50.

[13] Issa FG, Morrison DL, Hajduk E, et al. Digital monitoring of sleep disordered breathing using snoring sound and arterial oxygen saturation. Am Rev Respir Dis 1993;148:1023–9.

[14] Teramoto S, Matsuse T, Fukuchi Y. Clinical significance of nocturnal oximeter monitoring for detection of sleep apnea syndrome in the elderly. Sleep Med 2002;3:67–71.

[15] Baydur A, Behrakis PK, Zin WA, et al. A simple method for assessing the validity of the esophageal balloon technique. Am Rev Respir Dis 1982;126:788–91.

[16] Rechtschaffen A, Kales A. A manual of standardization terminology, techniques and scoring system for sleep stages of human subjects. Los Angeles, CA: BIS/BRI, UCLA; 1968.

[17] Anonymous, Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep 1999;22(5):667–89.

[18] Bonnet M, Carley D, Carskadon M, et al. EEG arousals: scoring rules and examples. A preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. Sleep 1992; 15:173–84.

[19] Watanabe T, Kumano-Go T, Suganuma N, et al. The relationship between esophageal pressure and apnea hypopnea index in obstructive sleep apnea–hypopnea syndrome. Sleep Res Online 2000;3:169–72.

[20] Drinnan MJ, Murray A, Griffiths CJ. Inter-observer variability in the assessment of EEG arousal. Thorax 1996;51(Suppl 3),A76:201.
[21] Horner RL, Brooks D, Kozar LF, et al. Immediate effects of arousal from sleep on cardiac autonomic outflow in the absence of breathing in dogs. J Appl Physiol 1995;79:151–62.
[22] Somers VK, Dyken ME, Mark AL, et al. Sympathetic nerve activity during sleep in normal subjects. N Engl J Med 1993;328:303–7.
[23] Schneider H, Schaub CD, Chen CA, et al. Effects of arousal and sleep state on systemic and pulmonary hemodynamics in obstructive sleep apnea. J Appl Physiol 2000;88:1084–92.
[24] Morgan BJ, Crabtree DC, Puleo DS, et al. Neurocirculatory consequences of abrupt change in sleep-state in humans. J Appl Physiol 1996;80:1627–36.
[25] Hornyak M, Cejnar M, Elam M, et al. Muscle sympathetic nerve activity during sleep in man. Brain 1991;114:1281–95.
[26] Oeverland B, Skatvedt O, Kvaerner KJ, et al. Pulseoximetry: sufficient to diagnose severe sleep apnea. Sleep Med 2002;3:133–8.
[27] Parrino L, Boselli M, Spaggiari MC, et al. Cyclic alternating pattern (CAP) in normal sleep: polysomnographic parameters in different age groups. Electroencephalogr Clin Neurophysiol 1998; 107:439–50.
[28] Collard P, Dury M, Delguste P, et al. Movement arousals and sleep-related disordered breathing in adults. Am J Respir Crit Care Med 1996;154:454–9.
[29] Terzano MG, Parrino L. Origin and significance of the cyclic alternating pattern (CAP). Sleep Med Rev 2000;4(1):101–23.
[30] Berlad I, Shlitner A, Ben-Haim S, et al. Power spectrum analysis and heart rate variability in Stage 4 and REM sleep: evidence for state-specific changes in autonomic dominance. J Sleep Res 1993;2: 88–90.
[31] Otzenberger H, Gronfier C, Simon C, et al. Dynamic heart rate variability: a tool for exploring sympathovagal balance continuously during sleep in men. Am J Physiol Heart Circ Physiol 1998;275: H946–50.