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Diagnosis of Sleep Apnea by the Analysis of Heart Rate Variation: A Mini Review

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***Abstract*—Cyclic variation of heart rate (CVHR) associated with sleep apnea/hypopnea episodes has been suggested as a marker of sleep disordered breathing (SDB). This study examined the utility of ECG-based CVHR detection for diagnosing SDB using simultaneous polysomnography as the reference standard. We used a previously developed automated CVHR detection algorithm (autocorrelated wave detection with adaptive threshold, ACAT) that provides the number of CVHR per hour (CVHR index). The ACAT was refined using a polysomnographic database of 194 subjects with various severities of SDB and then, applied to a single channel ECG obtained during standard overnight polysomnography in 862 consecutive subjects referred for SDB diagnosis. Using multiple thresholds of CVHR index ≥38 and <27, positive and negative predictive values of 95.6% and 95.1%, respectively, were achieved for detecting and excluding subjects with apnea-hypopnea index (AHI) ≥30, leaving 58 (6.7%) unclassified subjects. Positive and negative likelihood ratios (LRs) were 97.3 and 0.23, respectively. Also, thresholds of CVHR index ≥29 and <7 provided 96.1% and 95.1% of positive and negative predictive values, respectively, for subjects with AHI ≥15 (LRs, 50.6 and 0.11), leaving 426 (49.4%) unclassified subjects. The CVHR correlated with the AHI (r = 0.86) and showed the limits of agreement with the AHI of 19.6 and -18.6. Automated detection of CVHR by the ACAT algorithm provides useful screening tool for both increasing and decreasing probability of moderate and sever SDB with adequate thresholds.**

I. Introduction

SLEEP disordered breathing (SDB) is a serious contemporary challenge to health and well-being [1, 2]. Studies have demonstrated that SDB increases the risk of hypertension [3], coronary artery disease [4, 5], stroke [6], diabetes [7], chronic kidney disease [8], depression [9], cognitive impairment, diminished quality of life [10] and motor vehicle crashes [11]. Despite these facts and the availability of effective treatments, at least 75% of the patients with SDB remain undiagnosed [12]. Establishing efficient medical and public health system for SDB screening is therefore an urgent concern.

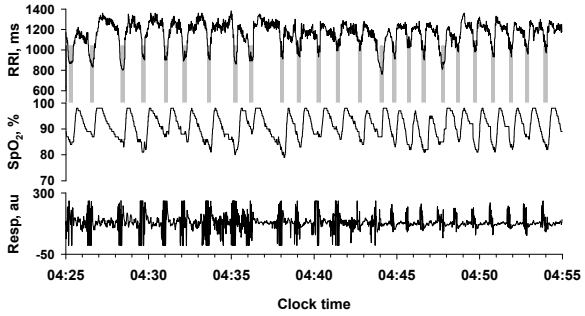

Fig. 1. Cyclic variation of heart rate (CVHR) and its detection by the algorithm of autocorrelated wave detection with adaptive threshold (ACAT) in a subject with obstructive sleep apnea and hypopnea. Gray vertical bars on R-R interval trend graph show the positions of individual episodes of CVHR (dips of R-R interval occurring on the resumption of breathing).

For this purpose, ECG monitoring during sleep may be promising. Episodes of SDB are accompanied by a characteristic heart rate pattern, known as cyclic variation of heart rate (CVHR) [13], which consists of bradycardia during apnea followed by abrupt tachycardia upon its cessation (Fig. 1). Earlier studies have demonstrated that this pattern can be used to detect SDB and suggested that the analysis of Holter ECG during sleep may be used as a screening tool for SDB [14-17]. However, most of these studies were based on observations in a limited number of subjects (≤150), consisting of typical patients and normal subjects, and their primary outcome was classification performance between them. Performance of diagnostic tests depends on the definition of SDB (i.e., cutoff level for severity) and the disease prevalence (pretest probability). The diagnostic utility of ECG-based screening for SDB needs to be examined in a sufficient size of cohort consisting of consecutive subjects with using an adequate reference standard and appropriate measures of agreement [18].

We previously reported an ECG-based CVHR detection algorithm named autocorrelated wave detection with adaptive threshold (ACAT) [19]. The ACAT algorithm provides the CVHR index (CVHRI) as the number of CVHR per hour. In the previous study [19], we examined diagnostic accuracy of the algorithm with a single cutoff of CVHRI ≥15 to identify patients with an apnea-hypopnea index (AHI) ≥15. This method, however, may underestimate the diagnostic utility of CVHRI, because a large number of patients have index values

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around the usual cutoff point and their classification could change due to expected variability in the measurement. Furthermore, by dichotomizing results into simply positive and negative, a substantial proportion of information is lost, particularly information that could better classify a patients as having mild, moderate, or severe disease. In the present study, we therefore employed a multiple thresholds approach to obtain the best sensitivity to reduce the probability that a patient has SDB (false negative rate) and the best specificity to increase the probability of SDB (true positive rate). We evaluated the likelihood ratio (LR) for each threshold in detecting patients with moderate and severe SDB.

II. Methods

A. Subjects

We used standard overnight attended polysomnographic data in 1,193 consecutive patients who were referred to the Sleep Laboratory of the Fujita Health University Hospital between January 2005 and December 2008 for diagnostic evaluation of suspected SDB. Data were excluded if the subject 1) were <16 yr of age, 2) had an implanted pacemaker or 3) had persistent atrial fibrillation. Data were also excluded if the total length of analyzable ECG in the polysomnographic recording was <360 min.

The protocol of the present study was approved by the institutional review board of the Fujita Health University, Toyoake, Aichi, Japan and the Ethics Review Committee of the Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan.

B. Diagnostic Polysomnography

The polysomnograms were recorded in a dedicated sleep laboratory. Experienced sleep technologists supervised data acquisitions, and subsequently annotated the respiratory events. Apneas were defined as complete cessation of airflow ≥10 sec and hypopneas as reduction of respiratory signals ≥10 sec associated with oxygen desaturation >4% and/or arousal. Obstructive and central events were distinguished by the presence or absence of paradoxical thoracic and abdominal movements during apnea or hypopnea.

C. CVHR detection

The single-channel digital ECG data were extracted from the polysomnograms at 100 Hz. All QRS complexes were detected and labeled as normal, ventricular ectopic, supraventricular ectopic, and artifact. The results were reviewed and all errors in beat detection and classification were corrected interactively by expert technicians of Holter ECG, who were blind to the polysomnographic diagnosis. Then, time series of R-R interval were generated using only consecutive normal QRS complexes and were interpolated at 2 Hz with a horizontal step function.

We applied the automatic ACAT algorithm on the interpolated R-R interval time series. In a previous study,[19] the ACAT algorithm was refined with the training polysomnographic data of 63 subjects with various severity of obstructive sleep apnea hypopnea. They did not include patients with central sleep apnea or periodic leg movement (PLM). Consequently, the previous version of ACAT algorithm was found to have limited ability to distinguish apnea-hypopnea episodes from PLM episodes. [19] In the present study, we therefore re-refined the ACAT algorithm with a polysomnographic database of 194 subjects including 40 patients with a central apnea index ≥10 and 30 patients with a PLM index ≥10. We used this new version of ACAT algorithm in the present study.

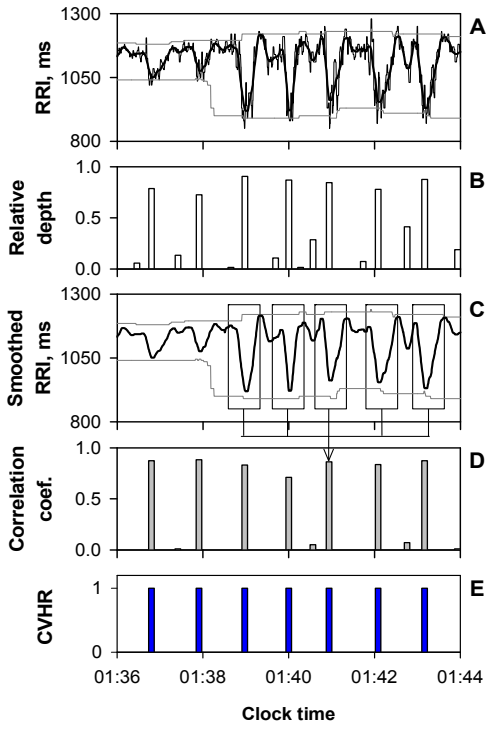

Fig. 2. Schema showing the methods for detecting CVHR by the ACAT algorithm. The ACAT detects the CVHR as cyclic and autocorrelated dips in R-R interval time series and determines the temporal position of the individual dips meeting the criteria for CVHR. The processes of the ACAT algorithm are as follows: R-R interval time series are smoothed by second-order polynomial fitting and the upper and lower envelopes of the R-R interval variations are calculated as the 95th and 5th percentile points, respectively, within a sifting window of 130-sec width (panel A). All dips in the smoothed trend with widths between 10 and 120 sec and depth-to-width ratios of >0.7 msec/sec are detected. Then, the dips meeting the following criteria are considered as CVHR: 1) a depth >40% of the envelope range at that point (panel B), 2) mean interdip interval (cycle length) of 4 consecutive dips between 29 sec and 120 sec, 3) a waveform similar to those of the two preceding and two subsequent dips with a mean morphological correlation coefficients >0.4 (panels C and D), and 4) three cycle lengths between four consecutive dips are equivalent with a tolerance of 22% against the mean cycle length. The number of dips meeting CVHR criteria per recording hour is defined as CVHR index (CVHRI).

The ACAT algorithm identifies individual CVHR as cyclic and autocorrelated dip in R-R intervals (Fig. 1). The processes of the algorithm are explained in the legend to Fig. 2 and the detailed procedure has been reported elsewhere [19]. The number of CVHR was counted as the number of dips

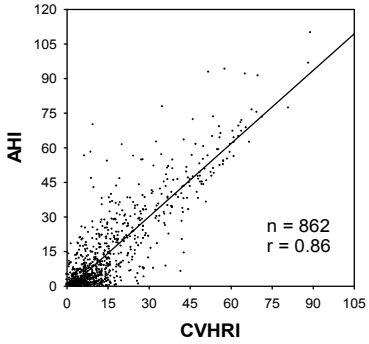

Fig. 3. Scatter graph with the regression line for the relationship between the apnea-hypopnea index (AHI) and the CVHR index (CVHRI) in 862 consecutive subjects referred for diagnosis for sleep disordered breathing (SDB).

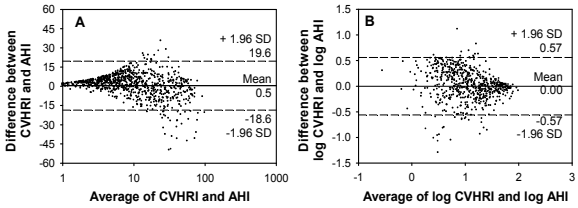

Fig. 4. Bland and Altman plot for the relationship between the AHI and the CVHRI in 862 consecutive subjects referred for diagnosis for SDB. Because the differences between AHI and CVHRI increased with AHI (panel A), a logarithmic transformation before the comparison was also used (panel B). Horizontal solid line and dashed lines indicate the mean difference and the upper and lower limits of agreement, respectively.

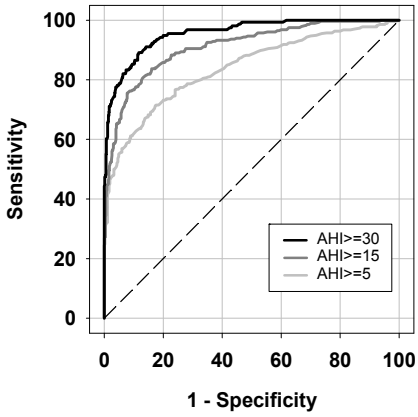

Fig. 5. Receiver-operating characteristic (ROC) curves of CVHRI for detecting subjects with SDB defined as the different thresholds of AHI. The dashed line indicates the position of ROC curve when a diagnostic test does not alter the pretest probability. The area under the curves (95% CI) for SDB defined as ≥30, ≥15, and ≥5 of AHI are 0.957 (0.941-0.969), 0.911 (0.890-0.929), and 0.838 (0.811-0.862), respectively (P <0.0001 for all).

meeting the criteria. The CVHRI was calculated as the mean number of CVHR per hour of time in bed.

D. Statistical Analysis

The American Association of Sleep Medicine (AASM) has published guidelines for assessing diagnostic alternatives to polysomnography [18]. According to the guidelines, we used Bland and Altman plots [20] for evaluating agreement between AHI and CVHRI, and used receiver-operating characteristic (ROC) curve analysis and LRs for assessing the utility of CVHRI for screening of SDB. Also, the guidelines allow for a "gray zone," where the result of screening test is accepted as "indeterminate." This offers an advantage over the commonly used single knife-edge threshold approach, as it does not penalize small errors due to expected variability. Accordingly, we adopted a multiple thresholds approach; one threshold for best reducing the probability that a patient has SDB (false negative rate) and the other threshold for best increasing the probability of SDB (true positive rate). These analyses were performed for three cutoff levels, 5, 15, and 30, of the AHI that correspond to mild, moderate, and severe SDB, respectively. To facilitate comparison with previous works, we also reported Pearson's product moment correlation coefficient.

TABLE I
PATIENT CHARACTERISTICS

n	862
Age, yr	49 ± 15 (16-83)
Female, *n* (%)	154 (18)
Body mass index, kg/m^2	27 ± 5 (16-47)
Time in bed, min	493 ± 24 (418-564)
AHI	15 ± 19 (0-110)
AHI ≥15, *n* (%)	280 (33)
4%ODI	13 ± 18 (0-104)
Minimum SpO_2, %	86 ± 5 (54-93)
PLM index	6 ± 15 (0-98)
PLM index ≥10, n (%)	150 (17)
Heart rate, bpm	62 ± 9 (45-89)

AHI = apnea-hypopnea index; PLM = periodic leg movement

TABLE II
CONFUSION MATRIX OF SUBJECTS CLASSIFIED BY AHI AND CVHRI

CVHRI	AHI		Total n (col %)	LR	*P*
	<30 n (row %)	≥30 n (row %)			
<27	679 (95.1)	35 (4.9)	714 (82.8)	0.23	0.05*
≥38	4 (4.4)	86 (95.6)	90 (10.4)	97.3	0.96*
Unclassified	23 (39.7)	35 (60.3)	58 (6.7)		0.60*
Total	706 (81.9)	156 (18.1)	862		0.18†

Data are the number of subjects (row %).
AHI = apnea-hypopnea index; CVHR = cyclic variation of heart rate; CVHRI = CVHR index; LR = likelihood ratio.
*Posttest probability of a subject to have an AHI ≥30.
†Pretest probability of a subject to have an AHI ≥30.

TABLE III
CONFUSION MATRIX OF SUBJECTS CLASSIFIED BY AHI AND CVHRI

CVHRI	AHI		Total n (col %)	LR	*P*
	<15 n (row %)	≥15 n (row %)			
<7	293 (95.1)	15 (4.9)	308 (35.7)	0.11	0.05*
≥29	5 (3.9)	123 (96.1)	128 (14.8)	50.6	0.96*
Unclassified	282 (66.2)	144 (33.8)	426 (49.4)		0.34*
Total	580 (67.3)	282 (32.7)	862		0.33†

Data are the number of subjects (row %).
AHI = apnea-hypopnea index; CVHR = cyclic variation of heart rate; CVHRI = CVHR index; LR = likelihood ratio.
*Posttest probability of a subject to have an AHI ≥15.
†Pretest probability of a subject to have an AHI ≥15.

III. Results

Of 1,193 eligible subjects, 319 (27%) were excluded because of poor ECG signal quality or an insufficient length (<360 min) of analyzable ECG. Additional 12 subjects were excluded due to atrial fibrillation during the polysomnographic recordings. Consequently, 862 subjects were included in the study cohort. Their characteristics are shown in Table I. The 331 excluded subjects did not differ significantly from the 862 included subjects in age (48 ± 16 yr), gender (female, 22%), BMI (27 ± 6 kg/m2), time in bed (494 ± 25 min), AHI (15 ± 20/h) or PLM index (5 ± 15/h).

The CHVRI closely correlated with the AHI (Fig. 3). The limits of agreement were 19.6 and −18.6 (Fig. 4). When logarithmic transformation was performed, the antilogarithms of the limits of agreement (−0.57 and 0.57) are 0.26 and 3.7, indicating that for about 95% of cases the CVHRI may differ from the AHI by 0.26 times below to 3.7 times above.

The ROC curve analysis revealed that CVHRI showed a good classification performance in identifying the patients with severe SDB (AHI ≥30) and those with moderate-to-sever SDB (AHI ≥15), while the performance was reduced when patients with mild SDB (AHI ≥5) were included (Fig. 5).

Using multiple thresholds of CVHRI ≥38 and <27, positive and negative predictive values of 95.6% and 95.1%, respectively, were achieved for detecting and excluding subjects with AHI ≥30, leaving 58 (6.7%) unclassified subjects (Table II). Positive and negative LRs were 97.3 and 0.23, respectively. Also, using thresholds of CVHRI ≥29 and <7, positive and negative predictive values of 96.1% and 95.1%, respectively, were achieved for subjects with AHI ≥15 (LRs, 50.6 and 0.11), leaving 426 (49.4%) unclassified subjects.

The presence of PLM was found to be a possible source of false positive. When the subjects with a PLM index >10 were excluded, positive predictive values of CVHR ≥38 and CVHR ≥29 for detecting subjects with AHI ≥30 and AHI ≥15 increased to 97.5% and 100%, respectively.

IV. Discussion

This study examined diagnostic utility of the automated CVHR detection by ACAT algorithm for SDB screening. Among 862 consecutive subjects referred for diagnostic polysomnography, we observed that CVHRI ≥38 and <27 were the useful diagnostic thresholds respectively for detecting and excluding subjects having severe SDB (AHI ≥30). By these thresholds, positive and negative predictive values of 95.1% and 95.6% were achieved, respectively, leaving only 6.7% of subjects as misclassified. Also, thresholds of ≥29 and <7 provided 95.1% positive and 96.1% negative predictive values for detecting and excluding subjects with moderate-to-severe SDB (AHI ≥15), when allowing for indeterminate results in 49.4% of subjects. Our results also suggest that the false positive rates may further reduce if subjects with PLM are excluded. These indicate that in subjects suspected to have SDB, the automated CVHR detection by the ACAT algorithm is a useful screening tool for both increasing and decreasing the probability of severe SDB and, in a half of subjects, it is also a useful screening tool for patients with moderate-to-severe SDB.

References

[1] T. Young, *et al.*, "Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort," *Sleep,* vol. 31, pp. 1071-8, Aug 1 2008.

[2] N. M. Punjabi, "The epidemiology of adult obstructive sleep apnea," *Proc Am Thorac Soc,* vol. 5, pp. 136-43, Feb 15 2008.

[3] P. E. Peppard, *et al.*, "Prospective study of the association between sleep-disordered breathing and hypertension," *N Engl J Med,* vol. 342, pp. 1378-84, May 11 2000.

[4] Y. Peker, *et al.*, "Increased incidence of coronary artery disease in sleep apnoea: a long-term follow-up," *Eur Respir J,* vol. 28, pp. 596-602, Sep 2006.

[5] A. S. Shamsuzzaman, *et al.*, "Obstructive sleep apnea: implications for cardiac and vascular disease," *JAMA,* vol. 290, pp. 1906-14, Oct 8 2003.

[6] M. Arzt, *et al.*, "Association of sleep-disordered breathing and the occurrence of stroke," *Am J Respir Crit Care Med,* vol. 172, pp. 1447-51, Dec 1 2005.

[7] N. M. Punjabi, *et al.*, "Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study," *Am J Epidemiol,* vol. 160, pp. 521-30, Sep 15 2004.

[8] J. J. Sim, *et al.*, "Sleep apnea in early and advanced chronic kidney disease: Kaiser Permanente Southern California cohort," *Chest,* vol. 135, pp. 710-6, Mar 2009.

[9] P. E. Peppard, *et al.*, "Longitudinal association of sleep-related breathing disorder and depression," *Arch Intern Med,* vol. 166, pp. 1709-15, Sep 18 2006.

[10] T. Young, *et al.*, "Epidemiology of obstructive sleep apnea: a population health perspective," *Am J Respir Crit Care Med,* vol. 165, pp. 1217-39, May 1 2002.

[11] S. Tregear, *et al.*, "Obstructive sleep apnea and risk of motor vehicle crash: systematic review and meta-analysis," *J Clin Sleep Med,* vol. 5, pp. 573-81, Dec 15 2009.

[12] T. Young, *et al.*, "Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women," *Sleep,* vol. 20, pp. 705-6, Sep 1997.

[13] C. Guilleminault, *et al.*, "Cyclical variation of the heart rate in sleep apnoea syndrome. Mechanisms, and usefulness of 24 h electrocardiography as a screening technique," *Lancet,* vol. 1, pp. 126-31, Jan 21 1984.

[14] T. Penzel, *et al.*, "Systematic comparison of different algorithms for apnoea detection based on electrocardiogram recordings," *Med Biol Eng Comput,* vol. 40, pp. 402-7, Jul 2002.

[15] A. H. Khandoker, *et al.*, "Support vector machines for automated recognition of obstructive sleep apnea syndrome from ECG recordings," *IEEE Trans Inf Technol Biomed,* vol. 13, pp. 37-48, Jan 2009.

[16] M. O. Mendez, *et al.*, "Automatic screening of obstructive sleep apnea from the ECG based on empirical mode decomposition and wavelet analysis," *Physiol Meas,* vol. 31, pp. 273-89, Mar 2010.

[17] F. Roche, *et al.*, "Analysis of the interbeat interval increment to detect obstructive sleep apnoea/hypopnoea," *Eur Respir J,* vol. 29, pp. 1206-1211, 2007.

[18] W. W. Flemons and M. R. Littner, "Measuring agreement between diagnostic devices," *Chest,* vol. 124, pp. 1535-42, Oct 2003.

[19] J. Hayano, *et al.*, "Screening for obstructive sleep apnea by cyclic variation of heart rate," *Circ Arrhythm Electrophysiol,* vol. 4, pp. 64-72, Feb 2011.

[20] J. M. Bland and D. G. Altman, "Statistical methods for assessing agreement between two methods of clinical measurement," *Lancet,* vol. 1, pp. 307-310, 1986.