Screening for Obstructive Sleep Apnea by Cyclic Variation of Heart Rate

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Background—Despite the adverse cardiovascular consequences of obstructive sleep apnea, the majority of patients remain undiagnosed. To explore an efficient ECG-based screening tool for obstructive sleep apnea, we examined the usefulness of automated detection of cyclic variation of heart rate (CVHR) in a large-scale controlled clinical setting.

Methods and Results—We developed an algorithm of autocorrelated wave detection with adaptive threshold (ACAT). The algorithm was optimized with 63 sleep studies in a training cohort, and its performance was confirmed with 70 sleep studies of the Physionet Apnea-ECG database. We then applied the algorithm to ECGs extracted from all-night polysomnograms in 862 consecutive subjects referred for diagnostic sleep study. The number of CVHR per hour (the CVHR index) closely correlated \( r = 0.84 \) with the apnea-hypopnea index, although the absolute agreement with the apnea-hypopnea index was modest (the upper and lower limits of agreement, 21 per hour and −19 per hour) with periodic leg movement causing most of the disagreement \( (P < 0.001) \). The CVHR index showed a good performance in identifying the patients with an apnea-hypopnea index \( \geq 15 \) per hour (area under the receiver-operating characteristic curve, 0.913; 83% sensitivity and 88% specificity, with the predetermined cutoff threshold of CVHR index \( \geq 15 \) per hour). The classification performance was unaffected by older age (\( \geq 65 \) years) or cardiac autonomic dysfunction (SD of normal-to-normal R-R intervals over the entire length of recording <65 ms; area under the receiver-operating characteristic curve, 0.915 and 0.911, respectively).

Conclusions—The automated detection of CVHR with the ACAT algorithm provides a powerful ECG-based screening tool for moderate-to-severe obstructive sleep apnea, even in older subjects and in those with cardiac autonomic dysfunction. (Circ Arrhythm Electrophysiol. 2011;4:64-72.)

Key Words: diagnosis ■ electrocardiography ■ heart rate ■ sleep apnea

Obstructive sleep apnea (OSA) is a syndrome characterized by repeated partial or complete obstruction of the upper airway during sleep, resulting in intermittent hypoxia and transient repetitive arousals from sleep. Recent prospective studies have reported that OSA is associated with an increased risk of fatal and nonfatal cardiovascular events, and this risk may be reduced by continuous positive airway pressure treatment.1–3 In patients with OSA, the repeated apneic episodes elicit increased sympathetic activation,4,5 surge in blood pressure,4,5 and cardiac arrhythmias.6–10 Concordant with this, the circadian distribution of sudden cardiac death among patients with OSA has a peak during the sleeping hours.11 OSA is also associated with hypercoagulability, vascular oxidative stress, systemic inflammation, and endothelial dysfunction.12 These facts indicate that diagnosis of OSA is essential in cardiovascular clinical practice. Definite diagnosis of OSA requires all-night laboratory polysomnographic examination, which is hard to perform in many patients because of its substantial cost and inconvenience and the potential risk of serious cardiovascular events during monitoring. The introduction of simple and efficient screening methods is necessary to identify patients with a high probability of OSA.

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For this purpose, ambulatory ECG monitoring during sleep may be promising. Episodes of OSA are accompanied by a characteristic heart rate pattern, known as cyclic variation of heart rate (CVHR), which consists of bradycardia during apnea followed by abrupt tachycardia on its cessation.13 Several earlier studies have demonstrated that this pattern can be used to detect OSA and suggested that the analysis of Holter ECG during sleep may be used as a screening tool for
OSA. However, most of these earlier studies were based on observations in a limited number of subjects (<150), consisting of typical OSA patients and normal subjects, and their primary outcome was classification performance between them. The CVHR has been reported to decrease among patients with autonomic dysfunction. Heart rate variations similar to CVHR also accompany periodic leg movements (PLMs) during sleep. Moreover, classification performance depends on the definition of OSA (ie, cutoff level for severity) and the proportion of patients (pretest probability).

To elucidate the usefulness of ECG-based screening for OSA, the relationship between CVHR and OSA severity must be studied quantitatively in controlled clinical settings.

In the present study, we examined whether the automated CVHR detection with ECG during sleep provides a useful marker for OSA screening. We developed a new automated algorithm, an autocorrelated wave detection with adaptive threshold (ACAT), for detecting individual CVHR events. After training the ACAT algorithm in independent samples, we applied the algorithm to ECG recordings during sleep in 1193 consecutive subjects referred for a diagnostic polysomnographic examination. We examined the correlation and agreement between the apnea-hypopnea index (AHI) and the CVHR as well as the ability of ACAT to identify patients with moderate-to-severe OSA.

### Methods

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.

#### Subjects

We studied the all-night polysomnographic recordings of 1193 consecutive subjects (the study cohort) referred to the Sleep Laboratory of the Fujita Health University Hospital between January 2005 and December 2008 for diagnostic evaluation of suspected sleep-disordered breathing. Subjects were excluded if they (1) were <16 year 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 minutes.

Controlled clinical settings.

We used 2 additional databases obtained from independent all-night polysomnograms. To refine our newly developed automated CVHR detection algorithm (ACAT), we used polysomnograms in 63 subjects (the training cohort). They were randomly selected from 364 (287 male and 77 female) subjects who were examined at the Sleep Laboratory of the Fujita Health University Hospital between January 2004 and December 2004 for a diagnostic evaluation of suspected sleep-disordered breathing. From the polysomnograms, a database was generated by extracting ECG, oxymoglobin saturation by pulse oximetry (SpO2), and oronasal airflow signals. The training cohort consisted of 55 men and 8 women between 18 and 86 years of age, with a body mass index of 26±6 (19 to 46) kg/m² and an AHI of 26±22 (0 to 91) per hour. All subjects were in sinus rhythm and free from PLM, and the length of recording was 454 to 596 minutes.

The other database we used was the open-access Physionet Sleep Apnea-ECG database (http://www.physionet.org/physiobank/database/apnea-ecg/), with which the methodological performance of the ACAT algorithm was tested. This database was generated for the Computers in Cardiology Challenge 2000. It consists of 70 single-lead ECG signals extracted from polysomnograms, with a length of 401 to 578 minutes, digitized at a sampling frequency of 100 Hz. Each recording has the annotation for each minute as to the presence or absence of sleep apnea during that minute. The subjects are 57 men and 13 women between 27 and 63 years of age, with a body mass index of 28±6 (19 to 45) kg/m² and an AHI of 28±28 (0 to 91) per hour.

### Polysomnographic Data

The polysomnographic recordings of the study and training cohorts were obtained using the Alice 3 and Alice 4 Diagnostic Sleep System (Philips Respironics, The Netherlands). The sleep stages, respiratory events, and PLM were scored using the standard diagnostic criteria of the American Academy of Sleep Medicine and a published criterion by registered polysomnogram technicians at the Sleep Laboratory of the Fujita Health University Hospital. Briefly, apnea and hypopnea were defined as the cessation or reduction of respiratory flow for ≥10 seconds caused by either airway obstruction (obstructive apnea) or lack of respiratory effort (central apnea) that was associated with at least 1 of the following: (1) ≥50% airflow reduction, (2) ≥3% oxygen desaturation, and (3) subsequent arousal. The AHI was determined for each polysomnographic recording as the mean number of apneas and hypopneas per hour of time in bed (TIB). The PLMs were defined as a series of ≥4 distinct leg movements, with an individual length of 0.5 to 5 seconds and an intermovement interval of 4 to 90 seconds, detected from the leg electromyographic recording. PLMs with a close temporal relation to apneas or hypopneas were not interpreted as PLMs. The PLM index was determined as the mean number of PLMs per hour of TIB.

In the present study, subjects with an AHI ≥15 per hour were considered to have moderate-to-severe OSA and those with a PLM index ≥10 per hour were considered to have significant PLM.

#### ECG Analysis

The single-lead digital ECG signals were extracted from the polysomnograms at a sampling frequency of 100 Hz. The ECG signals were scanned on a personal computer using a customized beat-detection and beat-classification algorithm that identified all QRS complexes and labeled the beats as normal, ventricular ectopic, supraventricular ectopic, and artifact. The results were reviewed, and all errors in beat detection and classification were corrected interactively on the computer screen by expert technicians of Holter ECG, who were blinded to the subjects’ polysomnographic diagnosis and other characteristics. To evaluate the cardiac autonomic nervous function, the SD of normal-to-normal R-R intervals over the entire length of recording (SDNN) was calculated. In this study, subjects with an SDNN <60 ms were considered to have cardiac autonomic dysfunction. For the purpose of CVHR detection, the R-R interval time series were interpolated with a horizontal-step function using only N-N intervals and resampled at 2 Hz.

### Automated CVHR Detection

For the automated CVHR detection, we developed a new algorithm by the method of ACAT (Patent application No. 2010–51387, Japan). This algorithm has been incorporated into a Holter ECG scanner (Cardy Analyzer, Suzuken Co, Ltd, Nagoya, Japan).

The ACAT algorithm is a time-domain method that uses only interbeat interval data. The algorithm detects the CVHR as cyclic and autocorrelated dips in smoothed interbeat interval time series and determines the temporal position of the individual dips comprising the CVHR (Figure 1 and Figure 2). The processes of the ACAT algorithm were as follows: Interbeat interval time series were smoothed by second-order polynomial fitting, and all dips in the smoothed trend with widths between 10 and 120 seconds and depth-to-width ratios of >0.7 ms/s were detected. Also, the upper and lower envelopes of the interbeat interval variations were calculated as the 95th and 5th percentile points, respectively, within a sliding window with a width of 130 seconds. Then, the dips that met the following criteria were considered CVHR: (1) a depth ≥40% of the envelope range at that point (adaptive threshold), (2) interdip intervals (cycle length) between 25 and 130 seconds, (3) a wave form similar to those of the 2 preceding and 2 subsequent dips with a mean morphological correlation coefficients ≥0.4 (autocorrelated wave),
and (4) 3 cycle lengths between 4 consecutive dips that meet the following equivalence criteria:

\[ \frac{3 - 2l_1/s}{3 - 2l_2/s}(3 - 2l_3/s) > 0.8, \]

where \( l_1, l_2, \) and \( l_3 \) are 3 consecutive cycle lengths and \( s = (l_1 + l_2 + l_3)/3 \).

In the present study, we counted the number of CVHR as the number of dips comprising the CVHR and calculated the CVHR index as the mean number of CVHRs per hour of TIB.

**Protocol**

The parameters of the ACAT algorithm were optimized using the data from the training cohort so that the best correlation and agreement were obtained between the AHI and the CVHR index. The cutoff threshold for the CVHR index was also determined in the training cohort as that corresponding with the highest average of sensitivity and specificity to identify subjects with moderate-to-severe OSA. The cutoff threshold was used as the predetermined cutoff threshold in the analysis that followed. We then applied the ACAT algorithm to the Physionet Apnea-ECG database to test the methodological performance of the ACAT algorithm and to compare it with the ECG-based OSA detection algorithms reported in earlier studies. The optimized ACAT algorithm was then used to detect CVHR in the study cohort. The CVHR detection was performed with the automated ACAT algorithm by a technician who was blinded to the subjects’ polysomnographic diagnosis and other characteristics.
Statistical Analysis
The correlation and agreement between the AHI and the CVHR index were evaluated with the Pearson product-moment correlation coefficient and Bland and Altman limits of agreement (95% confidence limits of overestimations and underestimations), respectively. The latter was calculated as the mean difference /H11006\1.96 SD of the differences between the AHI and the CVHR index. The significance of the difference in the levels of agreement between groups was evaluated by comparing the SD of the differences with an F test.

The classification performance of the CVHR index in identifying the subjects with moderate-to-severe OSA was evaluated by receiver-operating characteristic (ROC) curve analysis. The significance of the difference in classification performance between groups was evaluated by comparing the areas under the ROC curve (AUC) with the Hanley and McNeil method.\(^2\) The classification performance with a cutoff threshold was evaluated according to its sensitivity, specificity, positive predictive accuracy, and negative predictive accuracy. We considered a probability value <0.05 significant.

Results

Optimization of ACAT Algorithm in the Training Cohort
Figure 2 shows the strips of the R-R interval, SpO2, respiration (oronasal airflow), and the positions of CVHRs detected by the ACAT algorithm in 3 representative subjects with OSA in the training cohort. The ACAT algorithm reliably detected the temporal positions of individual CVHRs. It showed robustness to the changes in the amplitude and frequency of the CVHRs (Figure 2A), provided good detection even when the CVHR amplitude was very low (Figure 2B), and offered good discriminatory power from the physiological very-low-frequency component of heart rate variability (Figure 2C).

Figure 3 shows the relationship between the AHI and the CVHR index in the training cohort. The CVHR index closely correlated with AHI \((r=0.95, P<0.001)\) and the Bland and Altman plot showed that the upper and lower limits of the agreement were 13 and \(-13\) per hour, respectively. The ROC curve of the CVHR index for detecting subjects with moderate-to-severe OSA had an AUC of 0.913 (standard error, 0.011). The ROC curve analysis also indicated that the highest average of sensitivity (85%) and specificity (81%) was obtained with a cutoff threshold of CVHR index \(\geq 15\) per hour.

Detection Performance in the Physionet Apnea-ECG Database
Among the 70 subjects of the Physionet Apnea-ECG database, the correlation coefficients between the AHI and the CVHR index was 0.91, and the upper and lower limits of agreement were 23 and \(-23\), respectively. The AUC of the ROC curve analysis for the performance in identifying the subjects with moderate-to-severe OSA was 0.979 (standard error, 0.0127). With the cutoff threshold of CVHR index \(\geq 15\) per hour, the sensitivity, specificity, positive predictive accuracy, and negative predictive accuracy were 90%, 100%, 100%, and 88%, respectively. The presence or absence of CVHR in each minute agreed with the minute-by-minute annotation for sleep apnea for 83% of the total minutes.

Application to the Study Cohort
Of 1193 eligible subjects, 319 (27%) were excluded because of poor ECG signal quality or an insufficient length (<360 minutes) of analyzable ECG. An additional 12 subjects were excluded because of atrial fibrillation during the polysomnographic recordings. Consequently, 862 subjects were included in the study cohort. Their characteristics are shown in Table 1. The 331 excluded subjects did not differ significantly from the 862 included subjects in age \((48\pm16\text{ year})\), sex (female, 22%), body mass index \((27\pm6\text{ kg/m}^2)\), TIB.
Figure 3. Scatter graph with the regression line and Bland and Altman plot for the relationship between the AHI and the CVHR index obtained with the optimized ACAT algorithm in the training cohort. Horizontal solid line and dashed lines in the Bland Altman plot indicate the mean difference and the upper and lower limits of agreement, respectively.

The CHVR index obtained by the ACAT algorithm closely correlated with the AHI in the study cohort ($r=0.84$, $P<0.001$), although the absolute agreement was modest (upper and lower limits of agreement, 21 and 19 per hour, respectively; Figure 4A). The ROC curve analysis, however, showed a good performance in identifying the subjects with moderate-to-severe OSA (AUC of 0.913 (standard error, 0.0108) and indicated that the predetermined cutoff threshold of CVHR index $\geq 15$ per hour was useful (Figure 5).

To determine the factors affecting the relationship and agreement between the AHI and the CVHR index and the classification performance, we compared subgroups of subjects (Tables 2 and 3). Although the correlation coefficient was lower in the older subjects (age $\geq 65$ years) than in the younger subjects ($P<0.001$), neither the limits of agreement nor the classification performance were affected. The correlation, agreement, and classification performance were unaffected by the presence of cardiac autonomic dysfunction (SDNN $<65$ ms). The presence or coexistence of central sleep apnea (central sleep apnea index $\geq 1$ per hour) slightly increased the limits of agreement ($P<0.001$), toward an overestimation of AHI, although it did not reduce the classification performance. Among the subjects with a PLM index $\geq 10$ per hour, the correlation coefficient was decreased, the limit of agreement was increased toward an overestimation of AHI and the classification performance was reduced ($P<0.001$ for all).

PLM episodes were frequently associated with the cyclic changes in heart rate, many of which were detected by the ACAT algorithm as CVHR (Figure 6). Among 150 (17%) subjects with a PLM index $\geq 10$ per hour, 67 (45%) had no significant OSA (AHI $<5$ per hour). In these patients with PLM alone, 5158 episodes of CVHR were detected. These episodes were shorter in duration (dip width; $30\pm11$ seconds) and in cycle length ($44\pm16$ seconds) than the 66 760 episodes of CVHR ($36\pm12$ and $54\pm17$ seconds, respectively) observed in 227 subjects with increased OSA (AHI $\geq 15$ per hour) and no significant PLM (PLM index $<5$ per hour; $P<0.0001$ for both). Their distributions, however, overlapped considerably (Figure 7). Concordant with this, the removal of subjects with a PLM index $\geq 10$ per hour (n = 150) resulted in a substantial improvement in the AHI estimation with the CVHR index (Figure 4B).

Discussion

This is the first study to examine the ability of ECG-based automated CVHR detection to estimate the presence and severity of OSA in a large-scale clinical setting. Among the 862 subjects referred for a polysomnographic examination, we observed that the CVHR index obtained by the ACAT algorithm closely correlated with the AHI ($r=0.84$) and showed a good performance in identifying patients with moderate-to-severe OSA. Although the correlation between the AHI and the CVHR index was reduced in older subjects ($\geq 65$ years), the classification performance was maintained even in older subjects ($\geq 65$ years) and in subjects with

<table>
<thead>
<tr>
<th>Table 1. Characteristics of Subjects in the Study Cohort</th>
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<tbody>
<tr>
<td>n</td>
</tr>
<tr>
<td>Female, n (%)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
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<tr>
<td>TIB, min</td>
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<tr>
<td>AHI, per hour</td>
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<tr>
<td>AHI ≥15 per hour, n (%)</td>
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<tr>
<td>4%ODI, per hour</td>
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<tr>
<td>Minimum Spo₂, %</td>
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<tr>
<td>PLM index, per hour</td>
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<tr>
<td>PLM index ≥10 per hour, n (%)</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
</tr>
<tr>
<td>SDNN, ms</td>
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<tr>
<td>SDNN &lt;65 ms, n (%)</td>
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</tbody>
</table>

Data represent n (%) for categorical variables and mean±SD (range) for continuous variables.

BMI indicates body mass index; ODI, oxygen desaturation index.
cardiac autonomic dysfunction (SDNN < 60 ms). We observed, however, that the absolute agreement between the AHI and the CVHR index was modest and that the presence of PLM during sleep resulted in an overestimation of AHI. Given the adverse consequences of OSA, developing a simple and efficient screening tool for OSA is an urgent issue. Our observations are important for determining the usefulness and limitations of ECG-based screening for OSA.

Recently, several authors have developed algorithms for the automated ECG detection of OSA. Khandoker et al15 used a machine learning technique for automated recognition of OSA from wavelet analysis of R-R intervals and ECG-derived respiratory signal. They developed a classification algorithm using 83 training sets of sleep studies and applied it to 42 test studies selected from the Physionet Apnea-ECG database. The algorithm correctly recognized 24 of 26 OSA subjects and 15 of 16 non-OSA subjects. Mendez et al16 compared the empirical mode decomposition and the wavelet analysis for detecting OSA from the ECG signal. Using 25 training sets and 25 test sets of sleep studies generated from the Physionet Apnea-ECG database, they reported 85% accuracy for the empirical mode decomposition and 89% accuracy for wavelet analysis in classifying minute-by-minute apnea/nonapnea periods; both methods perfectly discriminated OSA patients from normal subjects. In the present

Table 2. Correlation and Agreement Between the AHI and the CVHR Index in the Subjects Grouped by Age and the Presence of Cardiac Autonomic Dysfunction, Central Sleep Apnea, and PLM

<table>
<thead>
<tr>
<th>Limits of Agreement†</th>
<th>n</th>
<th>R</th>
<th>SD of Difference*</th>
<th>Upper</th>
<th>Lower</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 65 years</td>
<td>717</td>
<td>0.84</td>
<td>10</td>
<td>21</td>
<td>−19</td>
</tr>
<tr>
<td>Age ≥ 65 years</td>
<td>145</td>
<td>0.76‡</td>
<td>11</td>
<td>25</td>
<td>−19</td>
</tr>
<tr>
<td>SDNN ≥ 65 ms</td>
<td>656</td>
<td>0.84</td>
<td>11</td>
<td>23</td>
<td>−19</td>
</tr>
<tr>
<td>SDNN &lt; 65 ms</td>
<td>206</td>
<td>0.81</td>
<td>10</td>
<td>20</td>
<td>−17</td>
</tr>
<tr>
<td>CAI &lt; 1 per hour</td>
<td>817</td>
<td>0.82</td>
<td>10</td>
<td>22</td>
<td>−18</td>
</tr>
<tr>
<td>CAI ≥ 1 per hour</td>
<td>45</td>
<td>0.88</td>
<td>12§</td>
<td>25</td>
<td>−20</td>
</tr>
<tr>
<td>PLM index &lt; 10 per hour</td>
<td>712</td>
<td>0.86</td>
<td>9</td>
<td>18</td>
<td>−17</td>
</tr>
<tr>
<td>PLM index ≥ 10 per hour</td>
<td>150</td>
<td>0.64‡</td>
<td>11§</td>
<td>27</td>
<td>−15</td>
</tr>
</tbody>
</table>

CAI indicates central apnea index.
*SD of the differences between the CVHR index and the AHI.
†Upper and lower limits of agreement of Bland and Altman plot (mean difference ± 1.96 SD of the differences).
‡Correlation coefficient significantly different from that of the rest of the subjects (P < 0.001).
§SD significantly different from that of the rest of the subjects, determined with F test (P < 0.001).
study, we observed comparable performances for the independently optimized ACAT algorithm in the Physionet Apnea-ECG database. Only a few studies, however, have been performed in clinical settings. Roche et al.17 proposed an increase in the relative power of very-low-frequency component (0.01 to 0.05 Hz) of interbeat interval increment (%VLFI) as a marker for OSA. Among a sample of 150 patients referred to a university hospital for clinically suspected OSA, the authors reported an AUC of 0.70 for identifying the patients with an AHI ≥15 per hour (n = 100) and 64% sensitivity and 69% specificity with using %VLFI ≥4% as the cutoff threshold.

The ACAT algorithm is unique among reported algorithms. Unlike the other algorithms that report OSA as the segment of time (typically 1 minute) that includes apnea/hypopnea episode(s), the ACAT algorithm provides the temporal position of each CVHR episode. This feature of the ACAT algorithm allowed us to predict the severity of OSA directly from the CVHR index. Moreover, the ACAT algorithm furnishes a time-local data adaptability with the local width of the envelopes of interbeat interval fluctuations as the reference for determining the amplitude threshold for CVHR.

Table 3. Classification Performance of the CVHR Index for Detecting Moderate-to-Severe Sleep Apnea in the Subjects Grouped by Age and the Presence of Cardiac Autonomic Dysfunction, Central Sleep Apnea, and PLM

<table>
<thead>
<tr>
<th></th>
<th>N (AHI ≥15 per hour, n (%)</th>
<th>AUC of ROC Curve (SE)</th>
<th>Sensitivity* %</th>
<th>Specificity* %</th>
<th>PPA* %</th>
<th>NPA* %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 65 years</td>
<td>717 (236 (33))</td>
<td>0.914 (0.0114)</td>
<td>82</td>
<td>88</td>
<td>77</td>
<td>91</td>
</tr>
<tr>
<td>Age ≥ 65 years</td>
<td>145 (44 (30))</td>
<td>0.915 (0.0298)</td>
<td>91</td>
<td>86</td>
<td>74</td>
<td>96</td>
</tr>
<tr>
<td>SDNN ≥ 65 ms</td>
<td>656 (228 (35))</td>
<td>0.912 (0.0121)</td>
<td>83</td>
<td>87</td>
<td>77</td>
<td>91</td>
</tr>
<tr>
<td>SDNN &lt; 65 ms</td>
<td>206 (52 (25))</td>
<td>0.911 (0.0262)</td>
<td>83</td>
<td>91</td>
<td>75</td>
<td>94</td>
</tr>
<tr>
<td>CAI &lt; 1 per hour</td>
<td>817 (255 (31))</td>
<td>0.908 (0.0115)</td>
<td>83</td>
<td>88</td>
<td>76</td>
<td>92</td>
</tr>
<tr>
<td>CAI ≥ 1 per hour</td>
<td>45 (25 (56))</td>
<td>0.969 (0.0201)</td>
<td>88</td>
<td>90</td>
<td>92</td>
<td>86</td>
</tr>
<tr>
<td>PLM index &lt; 10 per hour</td>
<td>712 (238 (33))</td>
<td>0.936 (0.0105)</td>
<td>83</td>
<td>94</td>
<td>88</td>
<td>92</td>
</tr>
<tr>
<td>PLM index ≥ 10 per hour</td>
<td>150 (42 (28))</td>
<td>0.799 (0.0390)†</td>
<td>86</td>
<td>61</td>
<td>46</td>
<td>92</td>
</tr>
</tbody>
</table>

CAI indicates central apnea index; NPA, negative predictive accuracy; PPA, positive predictive accuracy; and SE, standard error.

*Performance in detecting subjects with AHI ≥15 per hour with the predetermined cutoff threshold of CVHR index ≥15 per hour.

†AUC significantly different from that for PLM index < 10 per hour (P = 0.001).

Figure 6. CVHR accompanying PLM. Graphs showing the time series of R-R interval (RRI), oxygen saturation of pulse oximetry (SpO2), oronasal air flow (Resp), tibial electromyogram (EMGleg), and the temporal positions of CVHR detected by the ACAT algorithm in a representative subject with PLM. Respiratory trace and SpO2 show no apnea-hypopnea, whereas RRI shows cyclic variations.

Figure 7. Distributions of the duration (A) and cycle length (B) of CVHR. PLM alone accounts for data for 5158 episodes of CVHR detected in 67 subjects with PLM index ≥10 per hour and AHI < 5 per hour. OSA alone accounts for data for 66 760 episodes of CVHR detected in 227 subjects with AHI ≥15 per hour and PLM index < 5 per hour.
detection. This feature may contribute to the good classification performance in older (≥65 years) subjects and those with cardiac autonomic dysfunction. These factors have been reported to be associated with decreased CVHR amplitude and consequently, increased failure of detection.24

The Bland and Altman plot revealed that the absolute agreement between the AHI and the CVHR index was modest, with a tendency to overestimate in patients with central apnea and in those with PLM. The CVHRs accompanying the sleep apneas driven by respiratory control dysfunction are known to show highly predictable and almost metronomic patterns of oscillations, whereas those accompanying sleep apneas driven by anatomic dysfunction of the upper airway show more variable and irregular patterns of oscillations.25–27 Because of these features, the episodes of central sleep apneas may be detected more consistently with the ACAT algorithm than pure OSA episodes; this may have led to the tendency to overestimate in subjects with central apnea. In contrast, PLM episodes have been known to be accompanied by autonomic activations and heart rate changes consistent with CVHR.18,19 Although the CVHR associated with PLM has been reported to have a briefer duration, a more triangular shape, and a shorter cycle length than those associated with OSA,24 our observations suggest that both the duration (dip width) and the cycle length of CVHR associated with PLM and that associated with OSA may overlap considerably (Figure 7). To maintain the sufficient sensitivity to the CVHR associated with OSA, the optimized ACAT algorithm detected a substantial part of the CVHR associated with PLM, which may presents a possible methodological improvement for future studies.

Future studies must also address 2 important issues. First, in the present study, we studied subjects who were referred to the sleep laboratory of the university hospital for diagnostic polysomnographic examination. The performance of algorithm when applied to different populations, particularly those with a low pretest probability of OSA, is unclear. Given the needs for the OSA screening in general practice and health promotion, studies in the general population seem important. Second, we studied the ECG signal extracted from polysomnographic recordings obtained in the sleep laboratory. OSA detection may have been affected by the recording environment. To confirm the clinical usefulness of the method, appropriately controlled diagnostic studies comparing the CVHR index obtained with ambulatory ECG monitoring and the results of polysomnographic examination are also needed.

OSA is associated with increased risk for cardiovascular morbidity and mortality,1,2 and it may relate to important cardiovascular pathophysiologic mechanisms, including sympathetic activation,4,5 hypercoagulability, vascular oxidative stress, systemic inflammation, and endothelial dysfunction.12 Despite the adverse cardiovascular consequences of OSA, the majority of patients remain undiagnosed.28 The present study indicates that automated CVHR detection with the ACAT algorithm provides a powerful ECG marker for screening moderate-to-severe OSA even in older subjects and those with cardiac autonomic dysfunction. Although the challenge of handling PLM remains, our observations suggest the possibility that routine ambulatory ECG monitoring may be used as a screening tool for OSA by incorporating the automated algorithm into Holter scanners.

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Disclosures
Dr Hayano has applied for a patent on the ACAT algorithm (No. 2010–51387, Japan), which has been licensed to Suzuken Company Limited. K. Kawai is an employee of Suzuken Company Limited. Dr Kodama is an advisor to Suzuken Company Limited.

References
Recent prospective studies have reported that obstructive sleep apnea (OSA) is associated with an increased risk of cardiovascular events and this risk may be reduced by treatment. In patients with OSA, the repeated apneic episodes elicit increased sympathetic activation, surge in blood pressure, and cardiac arrhythmias. Concordantly, the circadian distribution of sudden cardiac death among OSA patients has a peak during the sleeping hours. Diagnosis of OSA, however, requires polysomnographic examination, which is hard to perform in many patients. Episodes of OSA are accompanied by a characteristic heart rate pattern, known as cyclic variation of heart rate (CVHR). Detection of CVHR by ambulatory ECG has long been suggested as a useful method for OSA screening, but no large-scale clinical study has been performed. In this study, we examined a new automated ECG algorithm called ACAT for its accuracy in detecting OSA. The ACAT was developed with 63 sleep studies in a training cohort, and its performance was confirmed with a published database (Physionet Apnea-ECG). It was then applied to 862 consecutive patients referred for diagnostic sleep study. The number of CVHR detected by the ACAT closely correlated \((r=0.84)\) with the apnea-hypopnea index. The CVHR \(\geq 15\) episodes per hour identified the patients with apnea-hypopnea index \(\geq 15\) with 83\% sensitivity and 77\% positive predictive accuracy. The classification performance was unaffected by older age \((\geq 65\) years) or cardiac autonomic dysfunction. Our study indicates that the automated detection of CVHR with the ACAT algorithm provides a powerful ECG-based screening tool for moderate-to-severe OSA.
Screening for Obstructive Sleep Apnea by Cyclic Variation of Heart Rate
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