Screening of Obstructive Sleep Apnea Syndrome by Heart Rate Variability Analysis

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Background—Enhanced nocturnal heart rate variability (HRV) has been evoked in sleep-related breathing disorders. However, its capacity to detect obstructive sleep apnea syndrome (OSAS) has not been systematically determined. Thus, we evaluated the discriminant power of HRV parameters in a first group of patients (G1) and validated their discriminant capacity in a second group (G2).

Methods and Results—In G1, 39 of 91 patients (42.8%) were identified as diseased by polysomnography, as were 24 of 52 patients (46%) in G2. Time-domain HRV variables (SD of NN intervals [SDNN], mean of the standard deviations of all NN intervals for all consecutive 5-minute segments of the recording [SDNN index], square root of the mean of the sum of the squares of differences between adjacent normal RR intervals [r-MSSD]), and SD of the averages of NN intervals in all 5-minute segments of the recording [SDANN]) were calculated for daytime and nighttime periods, as well as the differences between daytime and nighttime values (Δ[D/N]). Correlations between HRV variables and OSAS status were analyzed in G1 by use of receiver-operating characteristic (ROC) curves and logistic regression analysis. By ROC curve analysis, 7 variables were significantly associated with OSAS. After adjustment for other variables through multiple logistic regression analysis, Δ[D/N]SDNN index and Δ[D/N] r-MSSD remained significant independent predictors of OSAS, with ORs of 8.22 (95% CI, 3.16 to 21.4) and 2.86 (95% CI, 1.21 to 6.75), respectively. The classification and regression tree methodology demonstrated a sensitivity reaching 89.7% (95% CI, 73.7 to 97.7) with Δ[D/N] SDNN index and a specificity of 98.1% (95% CI, 86.4 to 100) with Δ[D/N] SDNN using appropriate thresholds. These thresholds, applied to G2, yielded a sensitivity of 83% using Δ[D/N] SDNN index and a specificity of 96.5% using Δ[D/N] SDNN.

Conclusions—Time-domain HRV analysis may represent an accurate and inexpensive screening tool in clinically suspected OSAS patients and may help focus resources on those at the highest risk. (Circulation. 1999;100:1411-1415.)

Key Words: sleep ■ heart rate ■ nervous system, autonomic

Obstructive sleep apnea syndrome (OSAS) is a growing health concern affecting up to 10% of middle-aged men.1 Today, its diagnosis depends on polysomnography recordings, which require a complex in-hospital technological medical environment. Despite the high cardiovascular morbidity and mortality associated with this syndrome, the substantial inconvenience and cost of polysomnography recordings may delay routine evaluation. The introduction of more simple screening tools could help recognize patients with high probabilities of OSAS and thus focus on candidates likely to be afflicted with this disorder. So far, of the parameters recorded on an ambulatory basis and compared with the yield of complete polysomnography, only pulse oximetry showed results consistent with disease severity.2 Abnormalities in nocturnal cyclical heart rate (HR) variations have previously been described in sleep-related breathing disorders.3 We hypothesized that a quantification using time-domain analysis of heart rate variability (HRV), which already demonstrated its usefulness in other clinical fields,4,5 could yield more pertinent diagnostic information because of better assessment of the autonomous nervous system activity. Thus, we chose to evaluate the sensitivity and specificity of this seemingly simple tool in patients referred to our clinic for OSAS diagnosis. We correlated HRV variables and diseased status assessed with complete polysomnography to establish pertinent HRV diagnosis thresholds in 1 group of patients; then, the selected HRV thresholds were applied to comparable patients to validate our findings.

Methods

Study Groups

The population under study consisted of patients referred to our university hospital for a polysomnography recording because of
clinically suspected OSAS. The first group, or the derivation set, consisted of 91 patients (71 men, 20 women) with a mean±SD age of 55.4±10.9 years (range, 30 to 78 years); the second group, or the validation set, consisted of 52 patients (34 men, 18 women) with a mean±SD age of 52.7±12.1 years (range, 22 to 77 years). Exclusion criteria were permanent or paroxysmal atrial fibrillation or permanent pacemaker. All patients underwent both a full polysomnography recording and ECG Holter monitoring.

Sleep Study and Polysomnography Scoring
Patients of both groups underwent nocturnal polysomnography recording with standard methods. The presence and stages of sleep were monitored by use of 2 pairs of EEG leads (C3-A2, and O2-A1), 2 pairs of electro-oculographic leads, and chin electromyographic leads. Air flow was measured by an oronasal thermocoupler. Respiratory efforts were monitored by use of respiratory plethysmography with transducers placed around the chest and abdomen. Arterial oxygen saturation was continuously recorded by pulse oximetry (Criticare Systems Inc) during the entire night. The polysomnogram was scored manually according to standard criteria. Apnea was defined as the absence of air flow for >10 seconds in the presence of persistent respiratory efforts. Hypopnea was defined as the association of a reduction of ≥50% of the amplitude of respiratory efforts during ≥10 seconds and a decrease in arterial oxyhemoglobin saturation of ≥4%. The apnea/hypopnea index (AHI) was defined as the number of episodes of apnea and hypopnea per hour of sleep; the threshold to accept the diagnosis of OSAS was chosen as an AHI≥10; patients were thus classified as diseased (OSAS+) or nondiseased (OSAS−). Each episode of apnea was characterized by measuring apnea duration and mean and minimal arterial oxyhemoglobin saturation. Total sleep time, number and duration of REM periods, and number and duration of arousals were measured. Total duration of arterial desaturation was quantified as cumulative time with arterial oxyhemoglobin saturation <90%.

ECG Holter Monitoring HRV Analysis
The Holter tapes were analyzed on a StrataScan 563 (Del Mar) equipped with an HRV module. All variables were calculated for the 24-hour, daytime (2:30 to 9:30 PM), and nighttime (midnight to 7 AM) periods, and the differences between daytime and nighttime values (Δ[D/N]) were computed.

HRV was evaluated by use of time-domain analysis. To perform the analysis, each QRS complex was identified, and the length between each QRS complex (RR interval) was calculated. Only normal-to-normal beats were considered for analysis. Several parameters describing the differences between RR intervals were calculated:

- The square root of the mean of the sum of the squares of differences between adjacent normal RR intervals (r-MSSD), SD of NN intervals (SDNN), SD of the averages of NN intervals in all 5-minute segments of the recording (SDANN), and mean of the SD of all NN intervals for all consecutive 5-minute segments of the recording (SDNN index).

Statistical Analysis
Data were analyzed with StatView and JMP (SAS Institute) software. Differences were considered significant when P<0.05. Values are expressed as mean and 95% SD (mean±SD).

In group 1 (the derivation set), statistical analyses were performed to evaluate the ability of each variable to discriminate between diseased and nondiseased status. Thus, the dependent variable was diseased status (OSAS+/−). The independent variables analyzed were age, sex, body mass index (BMI), and for HRV variables, their day and night values and the differences between their day and night values (Δ[D/N]), as night mean HR, Δ[D/N] mean HR, night r-MSSD, Δ[D/N] r-MSSD, night SDNN, Δ[D/N] SDNN, night SDNN index, Δ[D/N] SDNN index, night SDANN, and Δ[D/N] SDANN.

Receiver-operating (ROC) curve analysis was used with calculation of the area under the curves (AUC). An AUC value of 0.5 means that the variable distributions are similar in both populations; conversely, an AUC value of 1.0 means that the 2 populations’ variable distributions do not overlap at all. Logistic regression models were used also to analyze the data via a simple logistic regression of the diseased status versus each of the covariates to confirm the previously performed ROC curve analysis. Multiple logistic regression analysis was then used to evaluate the strength of the association of each variable with diseased status after adjustment for the other variables. Also, the ORs were calculated individually for the same most significant independent variables.

Finally, a threshold value was determined for the most significant variables to obtain better separation power between diseased and nondiseased status. Determination of the threshold values was based on the classification and regression tree (CART) methodology, which allows continuous variables to be split into 2 groups. All possible values were considered, and the chosen value was the one that maximized the Gini impurity criterion. Sensitivity and specificity were also estimated against the diseased and nondiseased status with their simultaneous “exact” 95% CI, ie, the 95% CI for sensitivity and specificity.

In group 2 (the validation set), sensitivity and specificity were calculated for diseased and nondiseased status by use of the 3 most significant independent variables identified by CART methodology in group 1.

Results
In group 1, the diagnosis of OSAS was established in 39 of 91 patients (42.8%) through polysomnography recording. The clinical and time-domain HRV variables of OSAS+ and OSAS− patients are summarized in Table 1. There were no differences in clinical characteristics between OSAS+ and OSAS− patients; in particular, neither age nor BMI was helpful in separating the 2 populations. Mean night SDNN, mean night r-MSSD, mean night SDNN index, and night SDANN were significantly higher in OSAS+ patients, as well as absolute values of Δ[D/N] mean HR, Δ[D/N] SDNN, Δ[D/N] SDNN index, and Δ[D/N] r-MSSD. ROC curves (continuous data) were built for each HRV variable: 7 were able to separate OSAS+ from OSAS− status with statistical significance (P=0.03 to <0.0001; Table 2). Once the 7 variables were classified according to their AUC values, the absolute Δ[D/N] SDNN index appeared to be the most powerful separator (P<0.0001), followed by the night SDNN index, Δ[D/N] SDNN, night SDNN, Δ[D/N] r-MSSD, and night r-MSSD; for each of these variables, the absolute differences between the day and night values were more potent predictors than the night values alone. Finally, the difference between night and day mean HR was the last significant variable. None of the time-domain values calculated over the day period reached statistical significance.

For each continuous variable, the thresholds giving a chosen sensitivity or specificity were calculated (Table 3). For the most powerful variable, Δ[D/N] SDNN index, the 90% sensitivity threshold was −10 ms and the 90% specificity threshold reached −43 ms.

The highest separation power was obtained by use of the CART methodology for the most powerful variables to derive a threshold value with an optimal sensitivity or specificity (Table 4). We thus recognized Δ[D/N] SDNN index as an efficient tool for the detection of OSAS and Δ[D/N] SDNN as an efficient parameter to exclude OSAS. For the Δ[D/N] SDNN index variable, sensitivity reached 89.7% (95% CI, 73.7 to 97.7) with a threshold value of −11.1; for the Δ[D/N]
TABLE 1. Clinical and HRV Characteristics in Group 1 With or Without OSAS

<table>
<thead>
<tr>
<th>Head</th>
<th>OSAS+ (n = 39)</th>
<th>OSAS− (n = 52)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>55.9 ± 12.0</td>
<td>54.9 ± 10.0</td>
<td>NS</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>31 (79)</td>
<td>41 (79)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.7 ± 9.6</td>
<td>27.9 ± 7.9</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>6 (15)</td>
<td>6 (11.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>14 (36)</td>
<td>15 (29)</td>
<td>NS</td>
</tr>
<tr>
<td>MI, n (%)</td>
<td>1 (2.6)</td>
<td>3 (5.8)</td>
<td>NS</td>
</tr>
<tr>
<td>CHF, n (%)</td>
<td>4 (10)</td>
<td>3 (5.8)</td>
<td>NS</td>
</tr>
<tr>
<td>HRV characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day SDNN, ms</td>
<td>80.5 ± 27.3</td>
<td>79.2 ± 28.3</td>
<td>NS</td>
</tr>
<tr>
<td>Night SDNN, ms</td>
<td>102.2 ± 33.4</td>
<td>76.9 ± 26.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>∆[D/N] SDNN, ms</td>
<td>−21.7 ± 32.9</td>
<td>2.3 ± 20.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Day r-MSSD, ms</td>
<td>30.0 ± 37.1</td>
<td>26.7 ± 12.4</td>
<td>NS</td>
</tr>
<tr>
<td>Night r-MSSD, ms</td>
<td>48.5 ± 34.1</td>
<td>35.4 ± 18.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>∆[D/N] r-MSSD, ms</td>
<td>−18.5 ± 17.8</td>
<td>−8.7 ± 12.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day SDNN index, ms</td>
<td>41.8 ± 22.3</td>
<td>40.8 ± 15.4</td>
<td>NS</td>
</tr>
<tr>
<td>Night SDNN index, ms</td>
<td>78.3 ± 33.8</td>
<td>52.9 ± 22.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>∆[D/N] SDNN index, ms</td>
<td>−36.5 ± 27.7</td>
<td>−12.1 ± 14.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Day SDANN, ms</td>
<td>65.6 ± 23.6</td>
<td>64.4 ± 27.5</td>
<td>NS</td>
</tr>
<tr>
<td>Night SDANN, ms</td>
<td>56.6 ± 16.8</td>
<td>48.8 ± 16.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>∆[D/N] SDANN, ms</td>
<td>5.7 ± 38.3</td>
<td>16.5 ± 32.4</td>
<td>NS</td>
</tr>
<tr>
<td>Day mean HR, bpm</td>
<td>80.1 ± 11.8</td>
<td>79.1 ± 11.5</td>
<td>NS</td>
</tr>
<tr>
<td>Night mean HR, bpm</td>
<td>64.9 ± 8.7</td>
<td>67.7 ± 11.8</td>
<td>NS</td>
</tr>
<tr>
<td>∆[D/N] mean HR, bpm</td>
<td>15.2 ± 67.1</td>
<td>11.4 ± 46.1</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

SDNN variable, specificity reached 98.1% (95% CI, 86.4 to 100) with a threshold value of −34.1.

A separate simple logistic regression analysis of diseased versus nondiseased status was performed for each of the covariates to verify the ROC curve analysis and to select a reasonable subset of explanatory variables for further investigation. Maximum likelihood estimates were obtained for each of the important explanatory covariates (Table 5). These results confirmed the ROC analysis except for the ∆[D/N] mean HR.

With the use of a multiple logistic regression analysis, only 2 time-domain HRV variables appeared to be independently and significantly associated with diseased status. After adjustment for the other variables, ∆[D/N] SDNN index (P < 0.001) and ∆[D/N] r-MSSD (P < 0.01) remained significant predictors of OSAS (adjusted OR, 8.22 and 2.86; 95% CI, 3.16 to 21.4 and 1.21 to 6.75, respectively).

In group 2, neither BMI (28.7 ± 9.8) nor age (52.7 ± 12) was significantly different from group 1. Of the 52 patients, 24 (46%) were diagnosed as OSAS+ with complete polysomnography. The repartitioning of patients according to associated disease status (diabetes, hypertension, chronic heart failure, and ischemic heart disease) was similar to that of group 1; the threshold value of −11.1 for ∆[D/N] SDNN index determined a sensitivity of 83%, and the threshold value of −34.1 for ∆[D/N] SDNN determined a specificity of 96.5%.

Discussion

Time-domain HRV analysis appears to be a powerful tool in investigating OSAS, and the differences between day and night values of selected variables are more powerful predictors than their night values taken separately.

Guilleminault et al3 described a strong relationship between the longest apneic events in OSAS and the greatest swings, illustrating what they called cyclical variation HR. These authors already proposed using this feature as a screening tool in OSAS, but this has not been applied. Similarly, Le Heuzey et al13 described greater visual enlargement of the RR trend and a significantly higher difference between minimal and maximal HR during the night in OSAS patients than in control subjects. However, these data were not quantified according to the criteria of the classic time-domain analysis accepted today.2 Meanwhile, both studies suggested using this test as a tool for preliminary identification of OSAS independently of the assistance of a sleep laboratory. At that time, quantification of RR-interval variations were not automated. Quantification of RR-interval variability has recently become a common feature in Holter systems, allowing easy calculation of HRV scores.

Spectral analysis of HRV had already been proposed by Shiomi et al,14 who used it to evaluate the benefits of the prosthetic mandibular advancement treatment in OSAS patients; this treatment decreased the power of the very low frequencies without other spectral changes. Furthermore, they did not find any significant change in the time-domain
variables. Conversely, we found pertinent criteria in time-domain variables that allowed OSAS diagnosis by creating specific new variables with enhanced discriminant capabilities. These new variables were calculated as the intervals between the lowest and highest boundary values of 3 classic variables, benefitting from an increased contrast between day and night HRV values, particularly Δ[D/N] SDNN index and Δ[D/N] r-MSSD.

The physiological basis of the observed abnormalities lies in the struggle against upper-airway obstruction, first stimulation of the parasympathetic arm of the autonomous nervous system, followed by an abrupt sympathetic activation caused by the resultant hypoxia. Thus, at night, the alternate strong successive parasympathetic and sympathetic drives dramatically enhance RR variability; of course, this enhanced HRV does not correspond to an isolated increase in parasympathetic activity as in healthy subjects. By contrast, the diurnal HRV is known to be reduced in OSAS patients,15 and it has already been demonstrated to be associated with enhanced sympathetic nerve activity.15,16 We hypothesize that the contrast observed between day and night values resulted mainly from the combination of these 2 phenomena.

**TABLE 4. Threshold Values of HRV Variables With CART Methodology**

<table>
<thead>
<tr>
<th>Threshold Value</th>
<th>Gini Index</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Simultaneous 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ[D/N] SDNN index, ms</td>
<td>−11.1</td>
<td>0.132</td>
<td>89.7</td>
<td>61.5</td>
</tr>
<tr>
<td>Δ[D/N] SDNN, ms</td>
<td>−34.1</td>
<td>0.082</td>
<td>30.8</td>
<td>98.1</td>
</tr>
<tr>
<td>Δ[D/N] r-MSSD, ms</td>
<td>−2.5</td>
<td>0.060</td>
<td>89.7</td>
<td>42.3</td>
</tr>
</tbody>
</table>

The strength of our study was deriving and validating new variables to obtain a high sensitivity (89.7%) and high specificity (98.1%) in the diagnosis of OSAS by choosing appropriate thresholds. Clinical use of these criteria should depend both on the population of interest and on the purpose of the investigator, who may want to point toward a higher sensitivity or a higher specificity. A high sensitivity would allow exclusion of the threat of OSAS by use of a single Holter recording in patients at risk, such as obese cardiac patients, whereas a high specificity would help to increase the probability of the disease if performed as a pretest in polysomnography centers.

This method has several limitations. First, some clinical disorders, such as mellitus diabetes, sequelae of myocardial infarction, and chronic heart failure, present with a blunted autonomic reactivity. These disorders, especially heart failure, are quite often associated with OSAS.17 Although such disorders would favor false-negative diagnosis of OSAS by blunting HRV, we were able to classify correctly 8 of 10 OSAS patients in a population of 23 patients having congeneric heart failure (n = 7), myocardial infarction (n = 4), or diabetes mellitus (n = 12). Complete polysomnography also carries some inaccuracies18: transducer position, failure, and displacement; artifacts resulting from movement; and alteration of sleep because of the technical environment. Finally, whereas arterial oxyhemoglobin saturation monitoring appears to be the only reference tool to quantify the deepness of the arterial oxygen desaturation, this variable currently does not reach 100% sensitivity and specificity in OSAS detection because oxyhemoglobin desaturation can reflect other disorders or can be relatively moderate despite severe structural sleep disorders. In this context, HRV abnormalities could be a better representative of sleep-breathing disorders, identified as autonomic microarousals, than a pure apnea hypopnea index. However, our results of HRV analysis are difficult to compare to commercially available diagnosis systems associating snoring, arterial oxyhemoglobin saturation, and HR monitoring because the results of this last algorithm are not convincing and their recordings are limited to night.2

From a technical point of view, to be consistent in the comparison between our recordings, we selected the same diurnal and nocturnal periods of HRV analysis. A change in this methodological choice could eventually lead to different results. The threshold selected for the reference diagnosis of OSAS was 10 events per hour, the more commonly used threshold. Importantly, patients who have ≥30 events per hour are identified with the same HRV threshold value with a sensitivity of 96% and a specificity of 99.7%, values much higher than for patients with ≥10 events per hour. Such
patients are certainly candidates for specific long-term therapy, such as nocturnal nasal continuous positive airway pressure.

In summary, time-domain analysis of HR variability, used as the only criterion, could thus represent an efficient tool in OSAS diagnosis with a sensitivity of 90%. The ease of use and interpretation are also of interest because of the high prevalence of the disease in the general population and the need for repeated control.

References
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