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The pure effects of obstructive sleep apnea syndrome on cardiac autonomic functions: heart rate turbulence analysis

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Abstract. – OBJECTIVES: To demonstrate the pure effect of obstructive sleep apnea syndrome (OSAS) on cardiac autonomic function (CAF) using heart rate turbulence (HRT) parameters.

PATIENTS AND METHODS: A total of 64 patients with OSAS and 30 age- and gender-matched healthy subjects were enrolled. All subjects had normal coronary arteries and were free from diabetes mellitus (DM) and hypertension (HT). The HRT parameters (TO, turbulence onset; TS, turbulence slope) were obtained from 24-h ambulatory electrocardiogram (ECG) recordings. HRT parameters were compared between groups, and the relationship between HRT and the apnea-hypopnea index (AHI) was examined.

RESULTS: No between-group differences were found in age or gender. Mean TO was significantly higher in the OSAS group than in healthy controls (0.89 ± 0.5, -0.08 ± 0.26; $p < 0.001$; respectively). The mean TS did not differ between the two groups (2.81 ± 3.06 versus 3.14 ± 2.33; $p = 0.212$). The AHI was positively correlated with TO ($r = 0.845$, $p < 0.001$). The multiple logistic regression analysis revealed that after adjustment for other variables, TO was a significant and independent predictor of AHI, OR 2.394 (95% CI: 1.596-3.591).

CONCLUSIONS: HRT (TO in particular) is correlated with AHI. Thus, impaired HRT may be an important factor underlying the occurrence of arrhythmia and sudden cardiac death in patients with OSAS.

Key Words:
Obstructive sleep apnea syndrome, Cardiac autonomic function, arrhythmia, ambulatory ECG, turbulence onset, turbulence slope.

Introduction

Obstructive sleep apnea syndrome (OSAS) is a common disease among adults, and is strongly associated with increased risk for cardiovascular disease[1]. Previous studies have shown an increase in all-cause mortality in patients with OSAS[1]. Moreover, OSAS is highly correlated with risk factors for coronary artery disease (CAD) including obesity, diabetes mellitus (DM), and dyslipidemia, and is related to hypertension (HT), congestive cardiac failure, pulmonary HT, arrhythmia, and atherosclerosis[2].

OSAS is associated with arrhythmia and the risk of sudden cardiac death[3]. Several studies have reported a relationship between OSAS and cardiac autonomic dysfunction, suggesting that cardiac autonomic function (CAF) is impaired in patients with OSAS[4-6]. However, these studies included patients with overt atherosclerotic heart disease, DM, and/or HT, and failed to control for the well-established relationship between autonomic dysfunction and atherosclerosis, DM, and HT, a potential confounding factor of the relationship between OSAS and autonomic dysfunction. The reduced cardiac autonomic activity associated with cardiac arrhythmia is a pathophysiological mechanism that may link OSAS and cardiovascular mortality. However, the mechanisms underlying the cardiovascular complications associated with OSAS are not fully understood.

In the present study, we evaluated CAF by measuring heart rate turbulence (HRT) in patients with OSAS who did not have DM or HT and had a normal coronary angiographic examination. HRT is an assessment of cardiac autonomic tone, and impairment reflects cardiac autonomic dysfunction, in particular impaired baroreflex sensitivity, and reduced parasympathetic activity[7].

Patients and Methods

Population and Study Protocol

Sixty four OSAS patients (35 males; mean age 49.9 ± 6.6 years) and as a control group thirty

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age-gender matched healthy subjects (16 males; mean age 42.0 ± 6.1 years) were recruited to the study. The study group consisted of the OSAS patients with normal coronary angiographic examination, without DM and HT. The control group did not report any sleep disturbance or other problems with snoring, oral breathing, witnessed apnea, excessive daytime sleepiness. For screening purposes, the control subjects underwent the treadmill exercise test and echocardiography. They also completed the validated Epworth Sleepiness Questionnaire[8] to exclude those with suspected sleep disordered breathing. Similar to previous studies, polysomnography was not performed in the control group[9-12].

A complete physical examination was performed before the study. Routine 12-lead electrocardiography (ECG) and echocardiography of the patients was also evaluated prior to the ambulatory ECG monitoring. All the OSAS group subjects were free from the coronary artery disease as shown in the coronary angiography before the examination, and no subject was receiving any medication for CAD. All participants were asked to refrain from alcohol and caffeine-containing beverages and strenuous exercise for 24 hours prior to study and during 24-hour Holter recording. All smokers were also asked not to smoke cigarettes for at least 8 hours before the study and during Holter recording.

The presence of potential causes of impaired HRT including congestive heart failure, moderate or severe degrees of any valvular regurgitation or co-existent valvular stenosis, previous MI, angina or angina-like symptoms, hypertension and diabetes mellitus, were accepted as exclusion criteria. Those patients with pacemaker rhythm, atrial fibrillation (AF), left bundle branch block, right bundle branch block, any sign of ischemia on the initial ECG, and echocardiographic evidence of left ventricular hypertrophy, systolic dysfunction, wall motion abnormalities or pericardial disease, were also excluded from the study. All participants gave their informed consent, and the Institutional Review Board approved the study protocol.

Polysomnography

Full-night polysomnography (PSG) was performed in all patients by a computerized system (Somnostar alpha; Sensormedics, Anheim, CA, USA). Following variables were recorded: electrooculogram, electroencephalogram, electromyogram of sub mental muscles, and electromyogram of the anterior tibialis muscle of legs, an electrocardiogram and airflow (with an oro-nasal thermistor). Thoracic and abdominal respiratory, efforts were recorded using inductive plethysmography, and arterial oxyhemoglobin saturation by pulse oximetry with a finger probe. Arousals were scored according to accepted definitions based on the American Sleep Disorders Association criteria for measurements, definitions, and severity ratings of the Sleep Related Breathing Disorders Task Force Report[13]. Obstructive apneas were defined as the absence of airflow for longer than 10 s; obstructive hypopneas as a 50% decrease in airflow or a clear but lesser decrease in airflow if coupled with either a desaturation of > 3% or an arousal in the context of ongoing respiratory effort. The apnea-hypopnea index (AHI) was defined as the number of obstructive apneas and hypopneas per hour of sleep. Patients with an AHI ≥ 15 were considered as OSAS. Patients with sleep disorders, except OSAS, such as upper airway resistance syndrome (UARS), central sleep apnea syndrome (CSAS), periodic limb movement disorder (PLMD), or narcolepsy were excluded. All records were scored manually for sleep stage, arousals, apneas, and hypopneas.

Analysis of Heart Rate Turbulence

The 24-h ambulatory ECG recordings of all patients were analyzed to obtain the HRT parameters of turbulence onset (TO) and turbulence slope (TS). Recordings were performed with a GE Marquette SEER system digitizing at 125 samples per second (GE Marquette, Milwaukee, WI, USA). QRS detection, morphology classification (normal, aberrant, premature aberrant) and measurement of the RR interval were automatically performed by the system. All Holter files were reviewed and manually corrected. HRT analysis was performed on sequences of sinus RR intervals after ventricular premature beats (VPB). The evaluated sinus rhythm immediately before and after the VPB was free from any arrhythmia or other artifacts. The HRT after a VPB comprises two parameters: TO, which represents the initial acceleration (shortening of R-R intervals); and TS, which represents the subsequent deceleration (prolongation of R-R intervals). In mathematical terms, TO (%) (normal < 0) is the difference between the sum of the first two R-R intervals after the compensatory pause following a VPB and the sum of the last two R-R intervals preceding the VPB, divided by the sum of the

last two R-R intervals preceding the VPB. The TS (normal > 2.5 ms/R-R interval number) were accepted as the steepest slope of a regression line over any sequence of five consecutive RR intervals[14]. The HRT values measured for all convenient VPBs was accepted as the final HRT value to characterize the patient.

For the risk stratification, HRT values are classified into 3 categories:

1. Category 0: TO and TS are normal;
2. Category 1: one of TO or TS is abnormal;
3. Category 2: both TO and TS are abnormal.

If HRT cannot be calculated because no or too few suitable ventricular premature complex tachogram are found in the recording, patients who are in sinus rhythm are classified as HRT category 0[15-16].

Statistical Analysis

Parametric data were expressed as mean ± SD, and categorical data as percentages. All statistical procedures were performed using SPSS 15 (SPSS 15.0 for Windows, SPSS Inc., Chicago, IL, USA). Independent parameters were compared via independent samples t test. The Mann-Whitney U test was used to test parametric data without binomial distribution. Categorical data were evaluated by chi-square test as appropriate. Correlations were searched by Pearson's correlation. Variables, found to have significant differences in univariate analysis ($p < 0.1$) were evaluated for multicolinearity and then enrolled into multivariable logistic regression analysis (stepwise forward LR). A $p < 0.05$ was accepted significant, using two-sided comparisons.

Results

Groups were comparable for age, gender body mass index (BMI) and smoking habits. There was no significant difference between the two groups in resting heart rate and blood pressure. Left ventricular diastolic dimension and ejection fractions were similar. All study subjects had sinus rhythm. The mean heart rate was significantly higher in the OSAS group than in the control group on ambulatory ECG monitoring. Between the Holter parameters, the OSAS group patients had a significantly higher mean TO value than the control group, whereas mean TS value was smaller in the OSAS group than in the control group, but not significantly. Clinical, echocardiographic and 24-hours ECG characteristics of both groups are shown in Table I.

In heart rate turbulence analyses, turbulence onset values were > 0% in 48 patients in the OSAS group, and in 6 subjects in the control group ($p < 0.05$), turbulence slope values were < 2.5 ms/RRI in 20 patients in the OSAS group, and in 4 patients in the control group ($p < 0.05$). When HRT parameters were compared considering the risk stratification categories, there were significant differences between OSAS and control groups for all categories (Table II).

Considering the risk stratification categories, AHI score was 19.14 ± 4.08 in category 0, 28.31 ± 7.51 in category 1 and 32.06 ± 6.70 in category 2. A significant relationship was observed between the value of the AHI score and the risk stratification categories (r = 0.768, $p < 0.05$). A strong positive correlation was also found between the value of AHI and TO (r = 0.871, $p < 0.001$; Figure 1). After adjustment for other vari-

Table I. The comparison of general features, echocardiographic and Holter parameters between group 1 and group 2.

	OSAS group (n = 64)	Control group (n = 30)	p value
Age, years*	41.9 ± 6.6	42.0 ± 6.1	N.S.
Male gender, %	54.7%	53.3%	N.S.
BMI, kg/m^2*	27.54 ± 3.17	27.16 ± 3.22	N.S.
Smoking, %	10.9%	10.0%	N.S.
Heart rate, bpm*	82.25 ± 6.67	71.87 ± 7.44	$p < 0.001$
Systolic BP, mmHg	121.23 ± 8.31	120.12 ± 7.45	N.S.
Diastolic BP, mmHg	71.12 ± 6.45	70.23 ± 5.98	N.S.
LVEF, %*	61.32 ± 5.23	61.92 ± 5.68	N.S.
LVEDD, cm*	4.32 ± 0.31	4.28 ± 0.33	N.S.
TO, %*	0.89 ± 0.50	-0.08 ± 0.26	$p < 0.001$
TS, ms/beat*	2.81 ± 3.06	3.14 ± 2.33	N.S. ($p = 0.212$)

*Values are mean ± SD. (BMI: Body mass index; BP: Blood pressure; LVEDD: Left ventricular end-diastolic diameter; LVEF: Left ventricular ejection fraction; TO: Turbulence onset; TS: Turbulence slope).

Table II. HRT parameters were compared considering the risk stratification categories.

	OSAS	Control	*p* value
Category 0	21.9%, n: 14	73.3%, n: 22	< 0.05
Category 1	50.0%, n: 32	20.0%, n: 6	< 0.001
Category 2	28.1%, n: 18	6.7%, n: 2	< 0.001

ables through multiple logistic regression analysis, TO just remained significant independent predictors of AHI, with ORs of 2.394 (95% CI, 1.596 to 3.591).

Discussion

The main findings of the present study were that the OSAS group had a significantly higher mean TO compared to the control group, there were significant differences between the two groups when the HRT parameters were compared according to the risk stratification categories, and the AHI of the OSAS group was positively correlated with TO.

OSAS is characterized by several cardiac complications including myocardial infarction, arrhythmias, and sudden cardiac death[5,14]. The mechanism underlying these cardiovascular complications is not known. However, sleep apnea is related to prolonged episodes of hypoxemia, which can cause increased sympathetic tone and baroreflex dysfunction[1,17], and increased sympathetic activity and impaired cardiac autonomic function may be the primary factors underlying cardiac complications in patients with OSAS. We found that the mean TO was significantly higher in the OSAS group than in the control group. Blunted TO be an indicator of impaired cardiac autonomic function[18], which may contribute to the cardiovascular complications associated with OSAS and explain the occurrence of arrhythmia and sudden cardiac death in patients with OSAS. Furthermore, this finding may account for the increased risk of cardiovascular mortality in patients with OSAS, and the reduced incidence of cardiovascular mortality following OSAS treatment.

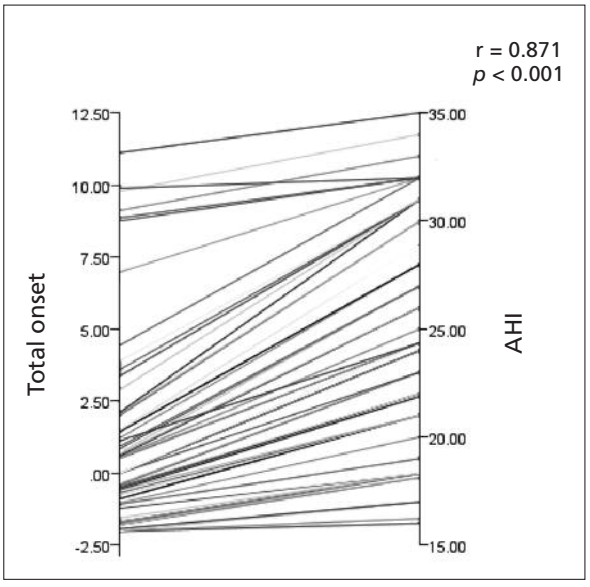

Figure 1. Positive correlation between the value of Apnea-Hypopnea index and Turbulence Onset.

Yang et al[19] reported that an abnormal TS was significantly correlated with the AHI in patients with OSAS, and Aytemir et al[20] demonstrated that both TO and TS were abnormal in patients with OSAS. We found similar data.

Previous studies have shown that impaired HRT is a significant predictor of mortality in patients with CAD[21,22]. Zuern et al[22] reported that HRT was a significant and independent risk predictor after myocardial infarction. Wustmann et al[28] concluded that baroreceptor stimulation caused sustained changes in HRT in patients with drug-resistant systemic HT. Furthermore, previous studies have shown a relationship between HT and blunted HRT parameters[24,25]. Balcıoglu et al[26] found that TO was significantly depressed in patients with type 2 DM, and a relationship between DM and impaired cardiac autonomic function has been reported[27,28]. Thus, the results of previous studies suggest that cardiovascular risk factors affect HRT parameters. To the best of our knowledge, this is the first report of CAF in patients with OSAS, controlling for confounding cardiovascular risk factors.

Conclusions

We compared 64 patients with OSAS who did not have CAD, DM, or HT to healthy control subjects. We found that the OSAS group had a significantly higher mean TO than the control group, and that the AHI of the OSAS group was positively correlated with TO. Previous studies of patients with OSAS may have found abnormal TO and TS because they included patients with CAD. Furthermore, an important methodological

difference between the present and previous studies is that we excluded CAD using angiography, whereas previous studies used symptoms or the exercise stress test.

The our study criticism to is that, we did not examine the impact of circadian variation. Therefore, diurnal fluctuations in autonomic tone suggest that measuring HRT at one time point in 24 h may not accurately reflect variability in heart rate.

OSAS is related to significant impairment in HRT. TO, in particular, has been reported to be correlated with the AHI. Our findings suggest that cardiac autonomic dysfunction is correlated with the severity of OSAS in patients without DM or HT.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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