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Increased myocardial vulnerability and autonomic nervous system imbalance in obstructive sleep apnea syndrome

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Summary
Background: Obstructive sleep apnea syndrome (OSAS) is characterized by the repeated episodes of upper airway obstruction during sleep, leading to significant hypoxia. Noninvasive evaluation of autonomic nervous system (ANS) and myocardial vulnerability may help determination of OSAS patients who are under high risk of malignant cardiac arrhythmias. The aim of this study was to show the effects of OSAS on predictors of arrhythmias by the evaluation of heart rate turbulence (HRT), heart rate variability (HRV) and QT dynamicity reflecting the ANS balance and myocardial vulnerability.
Methods: After polysomnographic study, 80 patients with OSAS and 55 age matched OSAS (−) subjects were included in the study. Twenty-four-hour Holter monitoring was performed in all subjects. HRT, HRV and QT dynamicity parameters were calculated.
Results: Turbulence slope was significantly decreased in OSAS patients whereas turbulence onset was increased ($P<0.001$). QT/RR slopes were significantly increased for QT end and QT apex ($P<0.001$). In HRV analysis, autonomic balance changed in favor of sympathetic system at night in OSAS patients. Furthermore, HRT and QT dynamicity parameters are found to be correlated with Apnea-Hypopnea Index (AHI).
Conclusion: OSAS is associated with a significant worsening in HRV, HRT, and QT dynamicity parameters. Our results may indicate that HRV and QT dynamicity parameters can be useful noninvasive methods that may detect autonomic nervous system activity and ventricular vulnerability in OSAS.

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Introduction

Obstructive sleep apnea syndrome (OSAS) is characterized by the repeated episodes of upper airway obstruction during sleep, leading to significant hypoxia. The prevalance of OSAS is mostly obtained by the cross-sectional studies. If the diagnosis of OSAS is based on the value of AHI >5, the prevalence is found to be 4% in males, and 2% in females.[1] It is associated with an increased rate of cardiovascular morbidity and mortality.[2] Some studies have demonstrated that OSAS predisposes to cardiac arrhythmias by causing autonomic nervous system (ANS) imbalance.[3,4] Noninvasive evaluation of ANS and myocardial vulnerability may help determination of patients who are under high risk of malignant cardiac arrhythmias. Newly evolving noninvasive evaluation techniques such as heart rate turbulence (HRT), heart rate variability (HRV), QT dynamicity based on 24-h electrocardiographic data may be useful in predicting risk in these patients.[5,6]

Heart rate turbulence is assessed by two parameters (turbulence onset and slope) derived from analyzing the fluctuation of RR intervals after a single ventricular premature beat (VPB). The turbulence onset indicates an overshoot decrease in the RR interval just after a VPB pause, and the turbulence slope indicates how fast the RR interval changes after the pause. HRT is a useful marker in patients with other heart diseases.[5]

The QT interval is formed by the combination of depolarization and repolarization, but since the depolarization time is short and constant compared to repolarization, changes in QT interval mainly reflects changes in repolarization. The QT interval adapts to changes in heart rate, so it is difficult to evaluate QT interval without correlating it with heart rate or RR interval. One way is to correct QT interval according to Bazett's formula.[7] However, QT intervals at identical RR intervals at day and night times show diurnal variation meaning circadian rhythmicity independent of heart rate.[8,9] Abnormal QT dynamicity, which means abnormal rate adaptation of ventricular repolarization, is an important predictor of myocardial vulnerability.[6] Ventricular repolarization abnormalities can reflect the influence of ANS on myocyte action potential.

The aim of this study was to show the effects of OSAS on predictors of arrhythmias by the evaluation of HRT, HRV and QT dynamicity reflecting the ANS balance and myocardial vulnerability.

Methods

The study population consisted consecutive patients referred to our sleep laboratory for clinically suspected OSAS. After polysomnographic study, 80 patients with OSAS and 55 age matched OSAS (−) subjects were included in the study. OSAS was diagnosed on the basis of polysomnographic recordings. HRT analysis after ventricular premature complexes was possible in 45 patients with OSAS and 24 subjects without OSAS. Exclusion criteria included atrial fibrillation, use of antiarrhythmic medication, and acute coronary syndrome (ACS) within 12 weeks, presence of diabetes and coronary artery disease. All patients and OSAS (−) group underwent a treadmill exercise test with Bruce protocol. The patients who had positive exercise test were also excluded from the study. Transthoracic echocardiographic examination was done to all subjects. Twenty-four-hour Holter monitoring was performed to all study populations. Recordings were obtained using 3-channel analog recorders and analyzed using the ELATEC Holter system. ELATEC Holter software was used to calculate HRT, HRV and QT dynamicity parameters. The investigators who analyzed the ECG parameters were blinded to OSAS (−)/patient status. The protocol of this study was approved by the Local Ethics Committee, and informed consent was obtained from every subject participating in this study.

Polysomnography

Overnight polysomnography was performed in all patients by a computerized system (Somnologica software) and included the following variables: electrooculogram, electroencephalogram, electromyogram of submental muscles, electromyogram of the anterior tibialis muscle of both legs, and electrocardiogram and airflow (with an oro-nasal thermistor). Chest and abdominal efforts were recorded using inductive plethysmography, arterial oxyhemoglobin saturation by pulse oximetry with a finger probe. Sleep stage were scored according to the standard criteria of Rechtschaffen and Kales.[10] Arousals were scored according to accepted definitions.[11] Apneas were defined as complete cessation of airflow $\geqslant 10$ s. Hypopneas were defined as reduction of $>50\%$ in one of three respiratory signals, airflow signal or either respiratory or abdominal signals of respiratory inductance plethysmography, or with a fall of $\geqslant 3\%$ in oxygen saturation or an arousal. The Apnea-Hypopnea Index (AHI) was defined as the number of apneas and hypopneas per hour of sleep. Patients with AHI <5 were included in OSAS (−) group. Subjects with AHI $\geqslant 5$ were considered as OSAS.

Analysis of HRT parameters

HRT parameters were calculated using the ELATEC Holter software. After a manual review of the recorded data, it was selected singular VPBs preceded and followed by $\geqslant 20$ normal sinus beats. The 20 subsequent RR intervals in the beats following a VPB were measured automatically and the HRT onset and slope were calculated according to the original method reported by Schmidt et al.[5] Turbulence onset (TO), reflects the initial phase of sinus rhythm acceleration, and turbulence slope (TS) describes the deceleration phase. Turbulence onset was defined as a percent difference between the mean of first 2 RR intervals after a ventricular premature beat and the 2 last sinus RR intervals before ventricular premature beats. Turbulence slope described a maximum positive slope of a regression line assessed over any of 5 consecutive RR intervals within the first 20 sinus RR intervals after ventricular premature beats. TO was calculated for all ventricular premature beats separately and then averaged, whereas TS was calculated based on an average local tachogram.[5]

Analysis of QT dynamicity parameters

Electrocardiographic data were obtained with a three channel analog recorder (ELA Medical Limited). After

manual review artifacts were deleted. Data analyzed with ELATEC holter software. The data was obtained during polysomnographic tests. Recordings were eligible if they had much more than 18 h of analyzable data. All 24 h periods were used to investigate QT dynamicity. The T apex was determined by fitting a parabola through the peak of the T wave, whereas the end of the T wave was determined by the intersection of the tangent of the downslope of the T wave with the isoelectric baseline. The software thereafter computed linear regression (QTend/RR and QTapex/RR) and provided the slope and correlation coefficient of these linear regressions. Measurements were obtained over the entire 24 h of recording. Analysis was performed by a single observer.

Analysis of heart rate variability parameters

For the HRV analyses, the definitions of evaluated parameters were made according to Task Force of European Society of Cardiology and the North American Society of Pacing and Electrophysiology on HRV.[10]

All 24 h, night- and day-time periods were used to investigate HRV parameters. For the time-domain analysis of HRV, each QRS complex resulting from sinus node depolarization is detected, and normal-to-normal (NN) intervals are determined.

The following standard parameters were calculated from the time series:

(1) SDNN: Standard deviation of intervals between two normal R-waves. SDNN gives an impression of the overall circulatory dynamics.
(2) RMSSD: The square root of square of mean square differences of successive NN intervals. Higher values indicate higher vagal activity.
(3) pNN50: The proportion derived by dividing NN50 (the number of interval differences of successive NN intervals greater than 50 ms) by the total number of NN intervals. Again higher values indicate higher vagal activity.

Spectral analysis of HRV included: total power, high-frequency (HF) component (0.15–0.40 Hz), low-frequency (LF) component (0.04–0.15 Hz), and very low-frequency (VLF) component (0–0.04 Hz). The normalized high-frequency power (HF nu $= 100 \times$ high-frequency power/total power), normalized low-frequency power (LF nu $= 100 \times$ low-frequency power/total power), and low /high-frequency power ratio (LF/HF ratio = low-frequency power/high-frequency power) were calculated to give the relative changes in HRV in the frequency domain.

Transthoracic echocardiography

Transthoracic echocardiographic examination were performed to all subjects by using a System Five (GE Vingmed Ultrasound, Horten, Norway) cardiac ultrasound scanner and 2.5–3.5 MHz transducers. LV end-diastolic (EDV) and end-systolic (ESV) volumes were computed as the maximum and minimal points on the LV volume waveform. EF was calculated independently for both apical views as (EDV−ESV)/EDV.

Statistics

Distribution of the continuous variables was determined by the Kolmogorov-Smirnov test, and all were found to be distributed normally, therefore parametric tests were performed. All numeric variables were expressed as mean $\pm$ SD, and categorical variables are expressed as percentages. Distribution of the numeric variables between groups was tested by using one-way analyses of variance method. Means were compared by ANOVA. The significance of correlations was assessed by Pearson correlation analysis. For all statistics, a two-sided P value <0.05 was considered statistically significant. SPSS for Windows version 10.0 statistical package was used.

Results

We studied 45 OSAS patients (mean age: 51 ± 9) and 24 OSAS (−) subjects (mean age: 50 ± 9, $P =$ NS). Baseline characteristics of the patients and the OSAS (−) group are shown in Table 1. There were no significant differences with respect to sex and age. All patients and OSAS (−) subjects had normal ejection fraction (67 ± 3, vs. 67 ± 4 respectively). No patient and OSAS (−) subject had diabetes, heart failure or chronic obstructive pulmonary disease before the investigation. Fourty-five percent of patients (20/44) and 42% of OSAS (−) subjects (10/24) were hypertensive, and using antihypertensive medications. All hypertensive patients had well-controlled hypertension. There was no statistically significant difference between OSAS patients and OSAS (−) subjects with regard to hypertension or antihypertensive medications. No subject had positive exercise test. The Apnea-Hypopnea Index was calculated as the number of apneas and hypopneas per hour of sleep. It was found to be significantly increased in OSAS patients compared with OSAS (−) subjects (25 ± 17, vs. 0.7 ± 0.2, $P<0.001$). Mean O_2 saturation during sleep was significantly decreased in OSAS patients compared with OSAS (−) subjects. There was no sustained ventricular and supraventricular arrhythmia in holter recordings. We found that there was no significant difference in VPB number/hour (13.1 ± 3.5 vs. 12.9 ± 2.3, $P =$ NS).

HRT parameters in patients and OSAS (−) subjects are listed in Table 2. Turbulence slope was significantly decreased in OSAS patients whereas turbulence onset was increased in OSAS patients (TS: 18.0 ± 4.2 vs. 11.3 ± 6.9, $P<0.001$; TO: -1.89 ± 1.38 vs. 1.64 ± 1.31, $P<0.001$). A negative relationship was found between TS and AHI ($r = -0.281$, $P = 0.019$). A positive relationship was found between TO and AHI ($r = 0.531$, $P<0.001$).

HRV parameters in patients and OSAS (−) subjects are listed in Table 3. SDNN in day time and all 24 h, RMSSD at night, LF/HF ratio in all 24 h were significantly decreased in OSAS patients, whereas, HFnu in all 24 h, HFnu, LFnu, LF/HF ratio at night, were significantly increased in OSAS patients. Both sympathetic and parasympathetic nervous system was found to be affected in OSAS but autonomic balance changed in favor of the sympathetic system at night. There was no significant relationship between any HRV parameters and AHI ($P =$ NS).

Table 1 Baseline characteristics and medications.

Characteristic	OSAS (+) ($n=45$)	OSAS (−) ($n=24$)	*P*-value
Age (mean ± SD)	51 ± 9	50 ± 9	NS
Male/female (no.−%)	34/11(76/24%)	19/5(79/21%)	NS
BMI (kg/m^2)	29.8 ± 4.4	26.3 ± 2.8	0.002
Ejection fraction (mean ± SD)	67 ± 3	67 ± 4	NS
Apnea-hypopnea index (mean ± SD)	25 ± 17	0.7 ± 0.2	<0.001
Mean SaO_2	91.1 ± 3.2	95.5 ± 2.1	<0.001
Heart rate (beat/min) in all 24 h	85 ± 9	70 ± 10	<0.001
Hypertension	20 (%45)	10 (%42)	NS
Medications			
• ACE inhibitor (no.−%)	12(26%)	5(21%)	NS
• CCB (no. −%)	8(18%)	5(21%)	NS

CCB: Calcium channel blocker, ACE: Angiotensin converting enzyme, BMI: Body mass index.

Table 2 Alteration of HRT and QT dynamicity parameters.

	OSAS (+)	OSAS (−)	*P*-value
Turbulence slope	11.3 ± 6.9	18.0 ± 4.2	<0.001
Turbulence onset	1.64 ± 1.31	−1.89 ± 1.38	<0.001
QT/RRapex slope	0.20 ± 0.05	0.15 ± 0.03	<0.001
QT/RRend slope	0.19 ± 0.05	0.14 ± 0.04	<0.001

QT interval dynamicity parameters (QT/RR apex and end slopes) are listed in Table 2. QT/RR slopes over 24 h were significantly increased for QT end and QT apex (QTapex/RR: 0.15 ± 0.03 vs. 0.20 ± 0.05, $P<0.001$; QTend/RR: 0.14 ± 0.04 vs. 0.19 ± 0.05, $P<0.001$). A positive relationship was found between QT/RR apex and AHI ($r=0.332$, $P=0.005$). There was no significant relationship between QT/RR end and AHI ($r=0.210$, $P=0.083$). A negative relationship was found between QT/RR apex-end and mean O_2 saturation ($r=-0.402$, $P=0.001$, $r=-0.274$, $P=0.03$). There was no correlation between medications and any HRT, HRV and QT dynamicity parameters. Also, hypertension was found not to have significant effect on HRT, HRV and QT dynamicity parameters. We did not find any additive effect of HRT to HRV and QT dynamicity in this patient population.

Table 3 Comparison of HRV parameters between subjects with and without OSAS.

	OSAS (+)	OSAS (−)	*P*-value
24 h			
SDNN (ms)	123 ± 30	140 ± 32	0.030
RMSSD (ms)	28 ± 14	33 ± 16	NS
PNN50 (%)	6 ± 5	9 ± 10	NS
24 h LF nu	35 ± 9	39 ± 9	NS
24 h HF nu	10 ± 5	7 ± 4	0.014
LF/HF ratio	3.50 ± 2.02	5.45 ± 2.26	0.008
Day time			
SDNN (ms)	89 ± 24	110 ± 26	0.001
RMSSD (ms)	25 ± 14	28 ± 15	NS
PNN50 (%)	4 ± 4	7 ± 9	NS
24 h LF nu	31 ± 12	32 ± 8	NS
24 h HF nu	8 ± 6	7 ± 4	NS
LF/HF ratio	3.88 ± 3.79	4.31 ± 2.15	NS
Night time			
SDNN (ms)	86 ± 22	98 ± 35	NS
RMSSD (ms)	32 ± 16	41 ± 18	0,036
PNN50 (%)	9 ± 10	15 ± 14	NS
24 h LF nu	58 ± 9	24 ± 12	<0.001
24 h HF nu	13 ± 5	8 ± 4	0.001
LF/HF ratio	4.46 ± 0.75	3.14 ± 1.72	0.017

SDNN: An impression of the overall autonomic activity.
RMSSD: Higher values indicate higher vagal activity.
PNN50: Higher values indicate higher vagal activity.
24 h HF nu: Higher values indicate higher vagal activity.
LF/HF ratio: Higher values indicate higher sympathetic activity.

Discussion

This study showed that OSAS was associated with a significant worsening of HRT, HRV and QT dynamicity parameters. A significant correlation was found between AHI and these parameters. We found that autonomic balance changes in favor of sympathetic system at night. In OSAS patients, hypoxaemia related to apnea and hypopnea may play an important role in these worsening. Hypoxemia may increase sympathetic nervous system activity via stimulation of carotid body chemoreceptors.[12,13]

The cardiac autonomic activity can be assessed by measuring HRV and HRT. Although blunted HRV is known to be a risk factor for arrhythmia generation there are several limitations of assessing HRV in OSAS. First HRV may be increased due to atrial end ventricular ectopic beats and second, respiration may have a confounding effect on HRV particularly on LF and VLF fractions. One of the main advantages of HRT compared to HRV is that HRV is not a convenient way of assessment of ANS activity in the presence of multiple VPBs. In persons with normal ANS balance, rapid change in heart rate in response to VPB

causes HRT. If there is an abnormality in ANS activity, this reaction weakens or disappears. Yang et al.[14] demonstrated that alterations in nighttime HRT correlate with the severity of sleep-disordered breathing, indicating abnormalities in cardiac autonomic activity in moderate-to-severe OSA even in the absence of overt cardiac disease. In our study, patients with OSAS had lower TS value and increased TO value. These results show abnormal ANS activity in OSAS patients, and may be an indicator of susceptibility to ventricular arrhythmias.

OSAS is characterized by repetitive partial or complete closure of upper airway during sleep and associated surges in sympathetic activity. Sleep is associated with dominant parasympathetic activity in normal subjects. This is a physiological response, and OSAS may alter this response.[4] Parasympathetic tone at the level of ventricular myocardium decreases in OSAS. Parasympathetic activity antagonizes sympathetic activity, shortens refractoriness and prevents ventricular fibrillation. HRV is a parameter reflecting the ANS activity on heart. HRV in relation to mean heart rate reflects changes in autonomic balance. Narkiewicz et al.[15] demonstrated that OSAS was associated with an increase in LF power and a decrease in HF power. Dingli et al.[16] showed that LF power increased around the episodes of hypopnea and apnea, concluding that sympathetic activity is elevated around respiration disturbances in patients with OSAS. We showed impairment of both some time domain and frequency domain parameters of HRV in OSAS. The LF/HF ratio at night, which represents sympatho-vagal balance, was significantly higher in patients with OSAS in our study. The changes in LF and LF/HF ratio suggest an increased sympathetic tone and discordance in sympatho-vagal activity in OSAS.

QT dynamicity is a surrogate measure of the cellular action potential, influenced by changing variables such as underlying heart rate, cardiac autonomic nervous activity, and the local ventricular electrical milieu. In this study, it was found significant worsening of QT dynamicity parameters in OSAS patients. This worsening strongly suggests increased myocardial vulnerability to arrhythmias. QT/RR slope reflecting the dynamics of repolarization is an important indicator in the risk stratification process together with myocardial dysfunction.[6] Since QT dynamicity reflects electrophysiological properties of ventricular myocytes in addition to ANS, it is believed that it carries additional prognostic value compared to HRV.[17] Several studies indicate that malignant ventricular arrhythmias and death may be associated with QT dynamics.[18,19] Chevalier et al.[20] showed that steeper slope of the QT/RR relationship was related to increased mortality after myocardial infarction. This may be due to facilitation of reentry by changes in refractoriness of myocardium. Roche et al.[21] demonstrated that OSAS patients had relative tachycardia compared to healthy subjects which was associated with enhanced nocturnal cardiac sympathetic drive. They also demonstrated that OSAS leads to flattened relationship between QT duration and RR slope. They postulated that impaired ANS may lead to altered rate dependent adaptation of myocardial repolarization, and autonomic neuropathy at the sinus node level in OSAS patients may further compromise electrical stability at the myocardial level. In OSAS, arterial oxygen desaturation and arousals are associated with sympathetic overactivity.

Javaheri[22] investigated the effects of continuous positive airway pressure (CPAP) on sleep apnea and ventricular irritability in heart failure patients. In OSAS patients, application of nasal CPAP resulted in improvement in disordered breathing and arterial oxygen saturation. Also, arousals from periodic breathing significantly decreased. In heart failure patients with OSAS, CPAP responders showed decrease in ventricular arrythmias in contrast to CPAP nonresponders. The reasons of improved ventricular irritability in CPAP responsive patients were explained by increased arterial oxygen saturation and decreased number of arousals in this study. In another study, Roche et al.[23] showed altered rate-dependent adaptation of myocardial repolarization in OSAS patients, and QT dynamicity was significantly improved with the treatment of OSAS in contrast to ventricular ectopic activity and static repolarization parameters. These studies imply that the evaluation of QT dynamicity is not only important for demonstrating the alteration in myocardial repolarization in OSAS, but also may be useful for the evaluation of response to the treatment.

Zareba[6] explained factors contributing to mortality in post infarction patients. Mortality in post infarction patients is related to abnormal ANS, myocardial substrate and increased myocardial vulnerability. Zareba stated that abnormal QT/RR slope is an indicator of increased myocardial vulnerability. In one study, the frequency of sudden cardiac death was found to be significantly higher in patients with OSAS than in persons without OSAS, than in general population, and than was expected by chance.[24] In that study, Gami et al. focused on the time pattern of sudden death from cardiac causes, and found that sudden cardiac death occurred during the sleeping hours, in contrast to the nadir of sudden cardiac death in persons without OSAS and in the general population. This was explained by the possible effects of nocturnal hypoxemia, cardiac ischemia and ventricular arrythmias. These findings imply that the myocardium is more vulnerable to arrythmia in OSAS.

Study limitations

This study is not a prospective study looking at arrhythmia incidence in OSAS patients, therefore future studies are necessary in OSAS patients for evaluation of arrhythmia incidence. Also, the prognostic implications of these parameters should further be evaluated.

HRV is highly sensitive in detecting differences in ventilation and breathing pattern within and across individuals.[25] For this reason the use of spectral analysis of HRV during nighttime should be limited to periods without apnea. At first glance, this may be thought to be a technical limitation. But we think that the evaluation of HRV during whole night period is acceptable including apneic episodes, because apnea, per se, is the main explanation for sympathovagal imbalance, and the degree of sympathovagal imbalance is directly related to apnea-hypopnea index.

Conclusions

OSAS is associated with a significant worsening in HRV, HRT, and QT dynamicity parameters. Furthermore, HRT and QT

dynamicity parameters are found to be correlated with AHI. In contrast to HRT, and QT dynamicity, nighttime HRV was not linked to the severity of OSA. Our results may indicate that HRV and QT dynamicity parameters can be useful noninvasive methods that may detect autonomic nervous system activity and ventricular vulnerability in OSAS.

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