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Original Article

Sleep apnea is related to prolonged QT interval and sleep hyperarousal is related to elongated Tp-e interval, regardless of acute autonomic impacts

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Objective: The aim of this study is to investigate if obstructive sleep apnea (OSA) or hyperarousal is associated with electrocardiac disturbances during ventricular repolarization via acute automatic impacts.

Methods: Natural-logarithm-transformed power values of heart rate variability (HRV) parameters were evaluated. In addition, values of heart-rate corrected QT interval (QTc), the interval between peak and end of T wave (Tp-e), and Tp-e/QTc ratio were calculated based on first 5-min arousal-free electrocardiography segment in pre-sleep-wakefulness (AWK), non-rapid-eye-movement stage 2 (N2), slow-wave (N3), and last rapid-eye-movement (REM) sleep from one-night polysomnographic data from 101 otherwise healthy males (43.5±7.9 yrs., 26.7±3.3 kg/m2; 17.7±18.3 and 33.0±17.6/hr apnea-hypopnea (AHI) and arousal indices (AI), respectively).

Results: Using linear regression analysis, QTc and Tp-e of all subjects at various stages were related to AHI and AI, respectively. Systolic, diastolic and mean arterial blood pressures at waking were all lower in low arousal groups than in medium or high arousal groups. There were no differences in blood pressure among the three groups based on AHI. No differences were found in the fluctuation of each HRV parameter across various stages among the three groups by AHI or AI values. QTc values at AWK, N2 and N3 were greater in severe OSA than in control subjects (468±40 vs 431±39; 469±46 vs 430±40; and 472±50 vs 434±41 ms; p values of 0.01, 0.01 and 0.02, respectively). Tp-e values sequentially decreased from high, medium to low arousal in AWK, N2 and N3 (117±15, 107±11, 107±16; 116±13, 108±15, 105±15; and 117±14, 109±14, 107±16 ms; p values of 0.00, 0.01 and 0.02, respectively) but Tp-e/QTc ratios were constant in both groups. Notably, while HRV spectral parameters fluctuated over various pre-sleep wakefulness and sleep stages as previously reported, QTc, Tp-e and Tp-e/QTc ratio remained static.

Conclusions: Severe OSA or hyperarousal subjects have a higher risk for ventricular arrhythmia around the clock related to prolonged repolarization and/or depolarization periods of ventricles which most likely results from long-term detrimental effects rather than acute autonomic impacts.

Keywords: Ventricular repolarization, sympathetic activity, cardiac arrhythmia

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Introduction

Characterized by loud snoring and repeated episodes of partial (hypopnea) or total collapse (apnea) of the upper airway during sleep, obstructive sleep apnea (OSA)[1] is the most common type of sleep disordered breathing in humans. Paralleling the severity of apnea and hypopnea index (AHI), OSA provokes various autonomic neuro-mechanic-hemodynamic changes[2], including repetitive arousals, intermittent sympathetic activities, large negative intrathoracic pressure fluctuations, and increases in cardiac pre- and after-load coincident with alterations in heart rate and arterial blood pressure. These real time impacts may underlie deadly nocturnal cardiovascular events including acute coronary artery disease, left ventricular dysfunction and possibly arrhythmia.[2, 3] Solely repetitive arousals[4] are coincident with sympathetic surges in OSA patients, which potentially cause electrical disturbances such as cardiac arrhythmias and even sudden cardiac death, especially during ventricular repolarization. Although numerous studies have indicated a link between OSA and cardiac arrhythmias[3], it remains unclear if patients with OSA have higher risk of sudden cardiac death. In fact, sudden death in patients with OSA may happen more often at night[5], implying certain harmful mechanisms or episodes during sleep. Thus, assessing cardiac sympatho-vagal balance in OSA patients during sleep is necessary to understand if OSA-related sudden death is related to instantaneous elevated cardiac sympathetic activity.

The spectral analysis of heart rate variability (HRV), determined by R-R intervals retrieved from electrocardiogram (ECG), provides a noninvasive means of measuring "quasi-real-time" cardiac autonomic activity. From these calculations, high-frequency (HF) power, ratio of low-frequency to HF (LF/HF), and very-low frequency (VLF) power represent vagal tone, sympatho-vagal balance and thermoregulatory modulation of cardiac electrodynamics, respectively[6-8]. Although focusing solely at the level of the sinoatrial node, this measurement identifies sleep-stage changes,[9] to predict cardiovascular prognosis,[6] and to clarify the severity of sleep apnea.[10] Changes in autonomic nervous activities can be measured within a short period of 5 minutes using this promising method, particularly during sleep when environmental confounding factors are minimized.

To understand the time period for ventricular myocardial repolarization - during which there is vulnerability to the development of reentry tachycardia, an ECG parameter, QT interval, was corrected for corresponding heart rate (i.e., QTc) using Bazett's formula.[11] This might reflect the refractoriness and electrical instability[12] of ventricular myocardium. The time interval between peak and end of T wave of ECG (Tp-e)[13] corresponds to transmural electro-dispersion of ventricular repolarization, exhibiting the propensity for ventricular arrhythmogenesis. Thus, value changes in these two surrogates of cardioelectric heterogeneity during sleep suggest ventricular arrhythmia in subjects with OSA and/or hyperarousal.

Cardiac arrhythmias[3, 14] are not uncommon in patients with OSA. However, only a few studies have been conducted that support a relationship between OSA and prolonged QT parameter (QT interval) on 24-hour Holter-ECG.[15] Long-term alterations in cardiac autonomic activity in OSA[2] may predispose toward ventricular arrhythmias by increasing the ventricular heterogeneity during repolarization. Rationally, the period of night sleep, when almost all extrinsic environmental confounders are inhibited, is the best time for evaluating the relationship between propensity of arrhythmias and real time fluctuations in autonomic nervous activities in patients with OSA and/or hyperarousals. This assumption is consistent with a previous finding[16] that the heterogeneity of ventricular repolarization can worsen during sleep. Notably, the time period of QT interval varies not

only with heart rate and circadian timing,[17] but also with gender.[18] In other words, higher values have been found in females when compared with males and during nighttime sleep when compared with other times[19]. It is conceivable that increased sympathetic activity[2] during repetitive arousals in OSA patients causes severe cardiac arrhythmias or even sudden cardiac death by myocardial electrical disturbances, particularly during ventricular repolarization. However, few studies have approached this issue.

We therefore hypothesized that the values of QTc and Tp-e are greater in male subjects with OSA or hyperarousal than in control subjects during night sleep, whereas the changes in these two ECG indices synchronize with cardiac automatic nervous activities over various ultradian sleep-wake stages. Accordingly, the value changes in QTc and Tp-e correspond to those of HRV parameters computed from segmented ECG data over pre-sleep wakefulness and various sleep stages from one night sleep polysomnography (PSG) in otherwise healthy male workers with diverse incidences of OSA and arousals.

METHODS

Subjects

This study was approved by the Medical Research Ethics Committee of our hospital. The subjects were male workers who underwent biochemical tests, cardiopulmonary exercise test (data shown but not analyzed intensely in this study), and PSG examination during regular annual physical from July 2007 to March 2010.

Inclusion criteria were male workers aged 30-65 years willing to enroll in this study. The exclusion criteria were documented conductive heart disease (such as atrial fibrillation or bundle branch block), abnormal renal, or thyroid function, abnormal serum electrolyte values, cardiac or collagen tissue complications, uncontrolled diabetes mellitus, regular or recent medication affecting heart rate (such as sympatho- or parasympathomimetics) or prolonging QT interval (antihistaminic or psychotropic medications or antibiotics), mental illness, neuromuscular disease, liquid protein or starvation diet, and any sign or symptom of heart failure, angina pectoris, or angina equivalent syndrome. In addition, participants were able to schedule ECG sessions and were eligible in terms of pre-sleep wakefulness and various sleep stage one-night PSG findings (see eligibility criteria for ECG data for HRV and QT interval processing). The data were not analyzed until written consent was received from the participants.

Experimental Protocol

All participants were requested to arrive at our lab between 8:00 pm and 9:00 pm for taking of medical history, physical examination and completion of questionnaire. Caffeinated foods or beverages were not allowed after lunchtime on the day of the study. Anthropometric assessments (measurements of body weight, height, and neck, waist and hip circumferences), pre- and post-sleep blood pressure measurements, and body mass index and mean arterial blood pressure calculations followed the procedures described in our previous study[20]. Sleep time was between 10:30 pm and 6:00 am and sleep was polysomnographically recorded.

Blood Pressure

Blood pressure was measured with a cuff sphygmomanometer in accordance with the recommendations of Russel et al.[21].

Sleep Polysomnography (PSG)

All PSG procedures and scoring standards of sleep parameters were based on the American Academy of Sleep Medicine Manual (The AASM Manual 2007), as in our previous study[20]. In brief, all sleep stages were scored by two well-experienced sleep technologists and further checked by a sleep specialist according to the electroencephalography (EEG) criteria defined by Rechtschaffen and Kales[22]. All signals from each 30s period of the PSG record were used to determine the sleep stages. A drop in airflow by ≥90% of baseline for at least 10s was defined as an episode of apnea. Excursions in oro-nasal pressure signal by ≥50% of baseline for ≥10s associated with ≥3% desaturation from pre-event baseline, or with

arousal, were defined as hypopnea.

AHI was defined as the average number of episodes of apnea and hypopnea per sleep hour. Arousal index (AI) was calculated as the number of EEG arousals per sleep hour. Individual leg movements were scored if duration was between 0.5 and 5 seconds and there was clear amplitude increase from baseline in leg channels. Periodic limb movement index (PLMI) was the average number of periodic leg movements per sleep hour. Other PSG parameters included total recording time, total sleep time, lowest oxygen saturation, oxygen desaturation index and duration of O2 saturation <90%, as well as percentages of total sleep time in REM (REM%), n-REM stage I (N1%), II (N2%), and slow wave (N3%) sleep.

Electrocardiography Signals

Consistent with the recommended procedures[6], preprocessing of the V2-lead-ECG signals was carried out by PSG at a sampling frequency of 256Hz. Data were included if total sleep time ≥3 hours, ECG recordings were ≥99% ectopic-free, and there were >6 min arousal-free ECG sessions in each of the four aforementioned stages. To avoid sleep stage transition effects and non-stationaries, we cut off the initial and final 30s portions and left 5 min ECG segment of each stage for HRV spectral analysis and QT calculation. Particularly, we considered pre-sleep wakefulness, post "lights-off" before falling asleep, instead of wake after sleep onset or morning awakening, as "awake state" (AWK) due to circadian rhythm concerns and to avoid the effect of sleep transitions. AWK was defined as the "first" 6 min proper ECG segment in AWK. We searched for the first AWK term. If not found, we searched for the next in the time sequence. This stepwise and forward time sequence search strategy was also applied to the search for segments in N2, and N3, whereas the "backward" in time sequence strategy was applied to find the "last" proper 6-min ECG segment in REM stage, denoted REM. All annotated segments of eligible ECG data from PSG recordings were processed by spectral analysis and used for QTc and Tp-e measurement and calculation.

QRS identifications were rechecked to avoid erroneous detections or missed beats. In terms of implementation of our computer algorithm: 1) The baseline of each 5 min ECG session, from the original 6 min arousal free segment, was adjusted to 0 volt. 2) After all negative voltage values in the session were replaced by 0 volt, the common threshold voltage level, higher than T wave peaks but lower than R wave peaks, was empirically set as mean voltage plus two standard deviations. 3) All R wave peaks were detected in the session during which voltages were higher than both the common threshold voltage and all rest points within a moving 0.2 sec. time window. 4) The 5 min ECG session was defined as eligible if within each of two consecutive RR intervals differences did not exceed 20%.

Spectral Analysis in HRV

On fast-Fourier transform analysis, the spectral power values of HF (0.15-0.40 Hz), LF (0.04-0.15 Hz), and VLF (0.003-0.04 Hz) were computed from 5-min segments of RR intervals [6] of the aforementioned stages. Notably, reliable values for the VLF band were available due to the 5-min long ECG segments corresponding to a resolution of 0.003 Hz.[23]

QTc and Tp-e Measurement and Calculation

To overcome the traditional difficulties associated with the detection of the T-wave terminus, we applied the algorithm proposed by Berger et al[22]. The operator defined a template QT interval following the rule below, and the algorithm then found QT intervals of all other beats by determining how much each beat must be scaled in time to best match the template. In this way, a robust estimation of QT interval was achieved without determination of each individual T-wave end. The QT intervals were 1) measured from the nadir of the Q wave to the end of the T wave (i.e., the return to TP isoelectric baseline using tangential method): 2) measured to the nadir of the curve between the T and U waves by a tangent aid if U waves were present. Tp-e interval was measured from the peak to the end of T wave. To verify the accuracy of these two algorithms, the timings of all R peaks, Q nadirs, and ends

Table 1. ***Anthropometric characteristics, blood pressure, pulmonary function parameters, peak exercise capacity, polysomnographic variables and biochemical data of all subjects and subjects divided into three groups: mild to moderate (M), severe (S) obstructive sleep apnea and normal control (Nor)***

	Total	Nor: AHI< 5	M: 5≦AHI< 30	S: AHI≧30		
n=	101	30	53	18	*p*	post hoc
AHI, events/hr	17.7±18.3	2.1±1.4	15.4±6.9	50.5±15.7		
Age, yrs	43.5±7.9	41.2±7.6	44.2±7.8	45.0±8.4	0.17	
BMI, kg/m2	26.7±3.3	25.3±1.7	27.0±3.5	28.0±4.1	0.01	S>Nor
Body height, cm	169.2±6.4	169.6±4.8	168.8±7.8	169.4±4.5	0.86	
Body weight, kg	61.8±21.5	60.5±19.2	63.2±21.2	59.8±21.5	0.78	
Neck, cm	53.0±18.3	49.9±19.2	52.0±18.1	61.3±18.3	0.09	
Waistline, cm	93.0±7.9	91.0±6.2	92.9±7.7	96.5±7.9	0.07	
Buttocks, cm	100.4±6.5	98.7±4.6	100.6±6.7	102.8±6.5	0.10	
Waist/Hip	0.93±20.2	0.92±0.05	0.92±0.05	0.94±20.2	0.50	
Waistline/Body height	34.1±19.5	34.6±26.5	36.6±27.6	26.1±19.5	0.38	
Smoking, n (%)	43 (42.6)	10 (33.3)	23 (43.4)	10 (55.6)	0.32	
Alcohol, n (%)	30 (29.7)	2 (6.7)	19 (35.8)	9 (50.0)	0.00	M,S>Nor
Regular exercise, n (%)	1 (1.0)	0 (0.0)	0 (0.0)	1 (5.6)	0.10	
FVCpre, %	91.7±12.1	90.6±8.8	92.1±13.7	92.5±12.5	0.84	
FEV1pre, %	89.6±11.9	90.3±10.0	89.5±13.4	88.5±10.5	0.88	
TLCpre, %	85.4±12.2	87.7±12.0	83.9±13.0	85.8±10.1	0.40	
DLCOpre, %	91.2±13.0	93.6±14.7	90.7±12.6	88.7±11.1	0.45	
MET, 3.5 mL/kg/min	5.9±1.8	5.8±2.1	6.0±1.6	5.9±2.0	0.95	
NSBP, mmHg	124.9 ± 13.5	125.7 ± 10.6	123.6 ± 15.6	127.4 ± 11.0	0.55	
NDBP, mmHg	79.2 ± 9.7	79.4 ± 10.0	78.5 ± 9.8	80.8 ± 9.3	0.68	
NMBP, mmHg	94.4 ± 9.4	94.8 ± 9.1	93.5 ± 9.7	96.3 ± 9.4	0.54	
DSBP, mmHg	123.7 ± 12.4	121.5 ± 11.5	122.7 ± 12.9	130.2 ± 10.8	0.04	
DDBP, mmHg	81.1 ± 10.5	79.0 ± 10.3	80.7 ± 10.9	85.8 ± 8.6	0.08	
DMBP, mmHg	95.3 ± 10.5	93.1 ± 10.2	94.7 ± 10.8	100.6 ± 8.9	0.05	
Total Sleep Time, min	364.0 ± 45.8	348.2 ± 48.5	373.3 ± 44.6	363.2 ± 38.7	0.05	
Sleep Efficiency, %	83.4 ± 7.8	82.0 ± 8.3	85.2 ± 7.0	80.4 ± 8.2	0.04	
Sleep Latency, min	16.7 ± 12.8	20.0 ± 17.1	14.4 ± 9.5	18.2 ± 12.0	0.14	
REM Latency, min	112.5 ± 54.7	117.8 ± 64.8	108.4 ± 52.4	115.5 ± 44.1	0.73	
N1%, %	6.7 ± 4.5	4.8 ± 2.7	6.5 ± 4.1	10.7 ± 5.6	0.00	S>Nor,M

N2%, %	51.3 ± 9.9	51.6 ± 12.9	51.4 ± 8.5	50.4 ± 8.0	0.91	
N3%, %	12.4 ± 7.5	13.8 ± 6.9	13.0 ± 8.1	8.0 ± 4.5	0.02	Nor,M>S
REM%, %	17.2 ± 5.6	16.3 ± 5.0	18.4 ± 5.9	14.9 ± 4.8	0.04	
Arousal Index, events/hr	33.0 ± 17.6	21.4 ± 10.9	32.4 ± 13.9	54.3 ± 17.7	0.00	S>M>Nor
Desaturation Index, events/hr	16.4 ± 15.8	2.5 ± 1.9	15.6 ± 8.3	41.7 ± 15.0	0.00	S>M>Nor
Lowest O2 Saturation, %	77.3 ± 11.8	87.2 ± 4.0	75.0 ± 10.4	67.5 ± 13.1	0.00	Nor>M>S
SaO2<90min, min	32.7 ± 55.2	3.6 ± 8.5	37.3 ± 66.0	67.9 ± 40.6	0.00	M,S>Nor
SaO2<90 Index, events/hr	5.5 ± 9.8	0.6 ± 1.3	6.2 ± 11.9	11.3 ± 7.4	0.00	M,S>Nor
PLMI, events/hr	7.1 ± 13.1	2.9 ± 6.2	10.3 ± 16.0	4.7 ± 9.6	0.03	M>Nor
Triglyceride, mg/dL	159.2 ± 88.7	141.0 ± 82.3	154.1 ± 81.3	204.5 ± 107.4	0.05	
HDL, mg/dL	2.7 ± 3.2	2.7 ± 3.0	2.8 ± 3.2	2.9 ± 4.5	0.99	
LDL, mg/dL	45.4 ± 8.4	46.4 ± 7.0	45.3 ± 8.6	44.0 ± 10.3	0.63	
Glucose, mg/dL	108.9 ± 28.8	104.9 ± 11.3	113.9 ± 38.0	102.4 ± 15.7	0.24	
Insulin, mg/dL	117.5 ± 31.6	118.4 ± 27.2	114.8 ± 34.8	123.5 ± 30.5	0.62	
HbA1c, mg/dL	8.7 ± 6.2	7.4 ± 5.2	8.3 ± 6.0	11.9 ± 7.5	0.04	
HOMA, mg/dL · mg/dL	245.0 ± 61.3	238.6 ± 56.3	238.0 ± 57.7	275.3 ± 72.8	0.08	
Uric Acid, mg/dL	6.4 ± 1.4	6.2 ± 1.2	6.4 ± 1.4	7.0 ± 1.3	0.13	
hs-C-Reactive Protein, mg/L	2.63 ± 3.18	2.67 ± 3.02	2.57 ± 3.07	2.86 ± 4.50	0.98	
ALT, mg/dL	35.8 ± 23.9	27.9 ± 13.6	37.6 ± 26.1	44.3 ± 28.1	0.06	
AST, mg/dL	24.3 ± 11.2	21.2 ± 6.6	23.9 ± 10.3	30.8 ± 16.6	0.02	S>Nor
Blood Urea Nitrogen, mg/dL	13.9 ± 3.2	13.4 ± 2.8	13.9 ± 3.7	14.6 ± 2.6	0.49	
Creatinine, mg/dL	1.0 ± 0.2	1.0 ± 0.1	1.0 ± 0.2	1.1 ± 0.1	0.52	

Nor: Normal; M: Mild-Moderate; S: Severe; FVCpre: Predicted Force Validation Capacity; FEV1pre: Predicted Forced Expiratory Volume in First Second; TLCpre: Predicted Total Lung Capacity; DLCOpre: Predicted Diffusing Capacity of the Lung for Carbon Monoxide; MET: Metabolic Equivalent; DSBP: Daytime Systolic Blood Pressure; DDBP: Daytime Diastolic Blood Pressure; DMBP: Daytime Mean Blood Pressure; NSBP: Nighttime Systolic Blood Pressure; NDBP: Nighttime Diastolic Blood Pressure; NMBP: Nighttime Mean Blood Pressure; PLMI: Periodic Limb Movements Index; HDL: High-density Lipoprotein; LDL: Low-density Lipoprotein; HOMA: Homeostasis Model Assessment; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase.

of T waves from raw ECG waves were visually inspected for overlap with corresponding R peaks from our computer algorithm. To compensate for the dependency of QT on heart rate, Bazett's formula ($QTc = QT/[RR^{1/2}]$)[11] was used to obtain heart rate-corrected values of QT intervals (QTc).

Statistics

Data are presented as mean±SD in tables and in the text, and as mean±SE in figures. To avoid skew distributions and to seek better fit, the spectral power values were natural logarithm transformed values. Linear regression testing was used to examine determinants of QTc and Tp-e in various

Table 2. ***Demographic and sleep polysomnographic parameters of all subjects related to QTc values in various stages using linear regression***

	Model 1			Model 2		
Variable: QTc	*B*	S.E.	*p*	B	S.E.	*p*
AWK						
(Constant)	474	24.0	0.00	456	22.2	0.00
Age	-0.95	0.51	0.07	-0.49	0.50	0.33
AHI	2.00	0.70	0.01	0.69	0.22	0.00
Arousal Index	0.14	0.32	0.66			
Desaturation Index	-2.09	0.83	0.01			
SaO_2<90 min	1.13	0.63	0.07			
SaO_2<90 Index	-5.22	3.45	0.13			
N2						
(Constant)	677	85.4	0.00	675	86.3	0.00
Age	-1.06	0.54	0.05	-0.63	0.53	0.23
AHI	1.79	0.75	0.02	0.82	0.23	0.00
Waist/Hip	-220	91.7	0.02	-230	90.82	0.01
Arousal Index	0.33	0.33	0.32			
Desaturation Index	-1.90	0.89	0.04			
SaO_2<90 min	1.10	0.66	0.10			
SaO_2<90 Index	-4.79	3.62	0.19			
N3						
(Constant)	489	25.8	0.00	470	24.0	0.00
Age	-1.30	0.55	0.02	-0.79	0.54	0.15
AHI	2.20	0.75	0.00	0.76	0.23	0.00
Arousal Index	0.25	0.34	0.47			
Desaturation Index	-2.40	0.90	0.01			
SaO_2<90 min	1.02	0.67	0.13			
SaO_2<90 Index	-4.44	3.72	0.24			
REM						
(Constant)	759	94.1	0.00	759	94.1	0.00
Age	-0.66	0.57	0.25	-0.66	0.57	0.25
AHI	0.66	0.25	0.01	0.66	0.25	0.01
Waist/Hip	-315	99.0	0.00	-315	99.0	0.00

Table 3. ***Demographic and sleep polysomnographic parameters of all subjects related to Tp-e values in various stages using linear regression***

	Model 1			Model 2		
Variable: Tp-e	*B*	S.E.	*p*	B	S.E.	*p*
AWK						
(Constant)	157	23.2	0.00	107	8.39	0.00
Age	-0.02	0.18	0.90	-0.07	0.18	0.71
Arousal Index	0.08	0.10	0.43	0.19	0.08	0.02
Lowest O_2 Saturation	-0.21	0.14	0.12			
Sleep Efficiency	-0.38	0.19	0.05			
N2						
(Constant)	155	23.4	0.00	109	8.39	0.00
Age	-0.10	0.18	0.60	-0.14	0.18	0.46
Arousal Index	0.09	0.10	0.37	0.19	0.08	0.02
Lowest O_2 Saturation	-0.20	0.14	0.16			
Sleep Efficiency	-0.34	0.19	0.08			
N3						
(Constant)	136	18.5	0.00	112	8.71	0.00
Age	-0.13	0.19	0.49	-0.16	0.19	0.40
Arousal Index	0.16	0.09	0.07	0.19	0.09	0.03
Sleep Efficiency	-0.30	0.20	0.14			
REM						
(Constant)	135	23.5	0.00	114	10.3	0.00
Age	-0.11	0.24	0.66	-0.27	0.22	0.23
Neck	-0.16	0.10	0.13			
Sleep Efficiency	-0.22	0.24	0.37			
Sleep Latency	0.29	0.15	0.06	0.37	0.14	0.01

stages in all participants for all demographic and PSG parameters of interest. One-way analysis of variance and post hoc analyses were applied to demographic characteristics, pulmonary function, exercise capacity, sleep PSG, biochemical data, and HRV spectral, QTc and Tp-e variables of three groups based on AHI or AI values (i.e., mild to moderate [M-], severe obstructive sleep apnea [S-] and normal control [Nor]; or low, moderate, or high frequencies of arousals [LA, MA, HA]). The paired t test was used to examine the differences in the neutral transformed spectral power values, QTc, Tp-e and Tp-e/QTc, between two stages. Statistical analysis was performed with SPSS version 20.0 (Scientific Packages for Social Sciences Inc., Chicago, Ill., USA). The level of significance was set at 5%.

Table 4. ***Significant differences in blood pressure, and polysomnographic variables among the three groups: Low Arousal (LA), Moderate Arousal (MA) and High Arousal (HA)***

n=	LA: AI<20 25	MA: 20≦AI<40 43	HA: AI≧40 33	*p*	post hoc
AHI, events/hr	5.4 ± 5.8	13.9 ± 10.4	32.2 ± 23.0		
DSBP, mmHg	117.3 ± 9.9	124.8 ± 12.4	127.0 ± 12.7	0.01	MA,HA>LA
DDBP, mmHg	75.5 ± 8.7	82.1 ± 10.3	84.0 ± 10.7	0.01	MA,HA>LA
DMBP, mmHg	89.5 ± 8.3	96.4 ± 10.0	98.4 ± 11.1	0.00	MA,HA>LA
N1%, %	3.2 ± 1.7	6.6 ± 3.1	9.5 ± 5.5	0.00	HA>MA>LA
N3%, %	16.4 ± 9.3	12.3 ± 6.2	9.4 ± 5.9	0.00	HA>LA
Arousal Index, events/hr	12.7 ± 3.8	29.5 ± 6.6	53.1 ± 12.2	0.00	HA>MA>LA
Desaturation Index, events/hr	5.2 ± 4.8	14.4 ± 11.0	27.5 ± 19.3	0.00	HA>MA>LA
Lowest O_2 Saturation, %	84.8 ± 6.1	77.4 ± 10.0	71.5 ± 14.2	0.00	LA>MA,HA
SaO_2<90min, min	12.0 ± 37.2	27.8 ± 39.3	54.9 ± 74.8	0.01	HA>LA
SaO_2<90 Index, events/hr	1.9 ± 5.7	4.4 ± 6.1	9.6 ± 14.1	0.01	HA>LA

RESULTS

Among 520 individuals completing annual physical, 101 eligible subjects were enrolled in this study. None of the subjects presented with cardiac disease that required treatment, including arrhythmia, except for 106 patients with hypertension. Table 1 lists the baseline demographics, blood pressure, electrocardiographic parameters (HRV, QT and their derivatives), various indices of one night sleep study, lung function, exercise test and biochemical data for all subjects and for the non-, mild to moderate, and severe OSA groups (n=30, 53, and 18 respectively). The subjects (Table 1; 43.5±7.9 yrs. at age, 26.7±3.3 kg/m^2 in BMI) demonstrated wide ranging AHI, AI, and Desaturation index (17.7±18.3, 33.0±17.6 and 16.4±15.8 events/hr, respectively).

AHI and Waist/Hip ratio were found to correlate with QTc in AWK, N2, N3 and REM and N2 and REM, respectively, with recruitment of various variables, except serum biochemical data, on linear regression analyses (Table 2). Accordingly, ANOVA and post hoc analyses of various variables among M, and S individuals and normal controls (Table 1) showed S>Nor for BMI, QTc, serum level of AST; S>M>Nor for AI and Desaturation Index; Nor>M>S for Lowest O2 Saturation; M>Nor for PLMI; M, S>Nor for alcohol consumption, duration and index of SaO2< 90; S>Nor, M for N1%; and Nor, M> S for N3%.

Similarly, arousal index and sleep efficiency were found to correlate well with Tp-e in AWK, N2 and N3 stages; and sole stage REM, respectively (Table 3). Participants were divided based on cutoff points of 20 and 40 events/hour into Low, Moderate, and High arousal groups (LA, MA, and HA; Table 4). HA>MA>LA was found for N1%, Desaturation Index. Both HA and MA showed higher systolic, diastolic and mean morning blood pressure than LA. HA>LA for alcohol consumption, and SaO2 desaturation in index and duration. HA>LA and MA for AHI and LA>HA for N3%. We investigated spectral HRV parameters and QTC, as well as their differences, in these three groups (based on AHI) in each stage (Table 5) (Fig. 1-d).

The values of RR interval (Fig. 1-a, b, c and 2-a, b, c) increased from AWK to N2 and further to N3 and REM in overall subjects, with similar changes over stages and in each stage in the three groups. Furthermore, the natural logarithm transformed values dropped from AWK to N2 and

Table 5. ***Various spectral HRV parameters, QTc, Tp-e and Tp-e/QTc in all subjects and among mild to moderate (M), severe (S) obstructive sleep apnea and normal control (Nor) groups in each stage.***

	Total	Nor: AHI<5	M: 5≦AHI<30	S: AHI≧30		
n=	101	30	53	18	*p*	post hoc
lnVLF						
AWK	6.3± 0.9	6.3 ± 0.9	6.4 ± 0.9	6.0 ± 1.1	0.29	
N2	5.8 ± 1.1	5.7 ± 1.0	5.8 ± 1.0	5.8 ± 1.5	0.87	
N3	4.8 ± 1.0	4.7 ± 1.0	5.0 ± 0.9	4.7 ± 1.1	0.30	
REM	6.6± 1.0	6.5 ± 1.0	6.6 ± 0.9	6.8 ± 1.2	0.56	
lnHF						
AWK	4.9± 1.1	4.9 ± 1.4	5.1 ± 0.8	4.5 ± 1.2	0.16	
N2	5.2 ± 1.2	4.9 ± 1.2	5.3 ± 1.2	5.2 ± 1.3	0.32	
N3	5.2 ± 1.2	5.0 ± 1.3	5.4 ± 1.2	5.0 ± 1.3	0.22	
REM	5.0± 1.4	4.6 ± 1.2	5.2 ± 1.5	5.1 ± 1.7	0.21	
lnLH						
AWK	0.56 ± 0.63	0.70± 0.73	0.52 ± 0.55	0.46 ± 0.69	0.35	
N2	0.43± 0.90	0.56± 0.80	0.38 ± 0.97	0.35 ± 0.87	0.62	
N3	-0.43 ± 0.97	-0.44 ± 0.81	-0.49 ± 1.08	-0.27 ± 0.91	0.72	
REM	0.75 ± 0.86	0.96± 0.78	0.63 ± 0.90	0.72 ± 0.87	0.25	
QTc						
AWK	446.7 ± 41.3	430.5 ± 39.0	448.5 ± 40.0	468.2 ± 40.0	0.01	S>Nor
N2	448.9 ± 44.6	430.3 ± 40.3	452.7 ± 43.3	469.0 ± 46.3	0.01	S>Nor
N3	449.6 ± 44.9	434.3 ± 41.0	450.7 ± 42.7	472.1 ± 49.5	0.02	S>Nor
REM	449.8 ± 48.2	435.9 ± 44.0	453.0 ± 47.3	463.3 ± 54.5	0.12	
Tp-e						
AWK	110.2 ± 14.7	107.5 ± 16.1	110.3 ± 14.2	114.5 ± 13.2	0.28	
N2	109.7 ± 14.7	105.7 ± 14.3	110.8 ± 15.5	113.4 ± 11.7	0.16	
N3	111.1 ± 15.3	108.0 ± 14.1	111.2 ± 16.1	115.9 ± 14.1	0.22	
REM	108.7 ± 17.7	108.0 ± 17.6	108.9 ± 16.6	109.3 ± 21.8	0.96	
Tp-e/QTc						
AWK	0.25 ± 0.03	0.25± 0.03	0.25 ± 0.03	0.25 ± 0.04	0.93	
N2	0.25± 0.04	0.25± 0.03	0.25 ± 0.04	0.25 ± 0.05	0.99	
N3	0.25± 0.04	0.25± 0.03	0.25 ± 0.04	0.25 ± 0.05	0.99	
REM	0.24 ± 0.04	0.25± 0.04	0.24 ± 0.04	0.24 ± 0.05	0.51	

Nor: Normal; M: Mild-Moderate; S: Severe; LH: Low Frequency/High Frequency.

further to N3, then rebounded from REM to AWK (Nor and M) or higher (S-subgroup), with levels

Table 6. ***QTc, Tp-e and Tp-e/QTc among Low (LA), Moderate (MA) and High (HA) Arousal groups in each stage.***

	LA: AI < 20	MA: 20≦AI <40	HA: AI≧40		
n=	25	43	33	*p*	post hoc
QTc					
AWK	441.1 ± 50.0	441.9 ± 37.4	457.1 ± 38.2	0.21	
N2	439.2 ± 51.1	445.5 ± 41.2	460.7 ± 42.5	0.15	
N3	440.6 ± 50.8	445.6 ± 41.0	461.8 ± 43.7	0.15	
REM	444.7 ± 53.3	446.3 ± 46.0	458.1 ± 47.4	0.48	
Tp-e					
AWK	106.6 ± 16.3	106.8 ± 11.0	117.4 ± 15.3	0.00	HA>LA,MA
N2	104.6 ± 15.2	108.2 ± 14.6	115.6 ± 12.7	0.01	HA>LA
N3	107.3 ± 16.4	108.8 ± 14.3	117.0 ± 14.2	0.02	
REM	106.7 ± 17.4	106.1 ± 15.0	113.6 ± 20.5	0.15	
Tp-e/QTc					
AWK	0.24 ± 0.03	0.24 ± 0.03	0.26 ±0.04	0.08	
N2	0.24 ± 0.04	0.24 ± 0.03	0.25 ±0.04	0.32	
N3	0.24 ± 0.03	0.25 ± 0.03	0.26 ±0.04	0.39	
REM	0.24 ± 0.04	0.24 ± 0.03	0.25 ±0.05	0.58	

LA: Low-arousal; MA: Moderate-arousal; HA: High-arousal; LH: Low Frequency/High Frequency.

surpassing those in AWK, N2 and N3 for lnVLF (Fig. 1-c). There were similar levels in AWK and N2, which dropped to N3 then surged to a level surpassing AWK or N2 for lnLH (Fig.1-b). ln(HF) values (Fig. 1-a) rose from AWK to N2 or N3 in S- or M-subgroup, then dropped back to REM. QTc values in AWK, N2 and N3 were greater in severe OSA patients than in normal controls (468±40 vs 431±39; 469±46 vs 430±40; and 472±50 vs 434±41 ms; p values of 0.01, 0.01 and 0.02 respectively; Table 5, Fig. 1-c), whereas Tp-e values sequentially decreased from high, medium and low arousals in AWK, N2 and N3 (117±15, 107±11, 107±16; 116±13, 108±15, 105±15; and 117±14, 109±14, 107±16 ms; p values of 0.00, 0.01 and 0.02 respectively; Table 6, Fig. 2-e). Notably, no differences in Tp-e/QTc ratio were found among groups categorized by either AHI or AI in any stage (Table 5 and 6; Fig. 1-f and 2-f).

DISCUSSION

Even though HRV spectral parameters present on sinoatrial node in quasi-real time manner, fluctuating over various pre-sleep wakefulness and sleep stages, they are not affected by AHI or AI, as reported previously[44]. QTc, Tp-e and Tp-e/QTc ratio did not oscillate over different ultradian stages. While QTc values in AWK, N2 and N3 were greater in severe OSA patients than in normal controls, Tp-e value, the index of transmural dispersion of ventricular repolarization, was larger in HA in AWK when compared with LA or MA and in N2 when compared with LA. However, no differences in Tp-e/QTc ratios were found among the groups categorized by either AHI or AI values. To the best of our knowledge, the current study is one of the few relating QTc, Tp-e and Tp-e/QTc ratio with HRV parameters over various sleep stages, in terms of the incidences of sleep apnea and night-sleep arousals. Our results not only

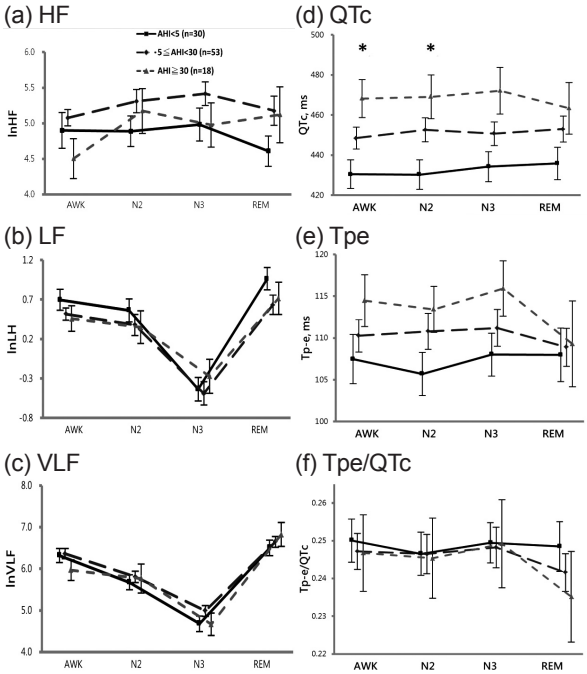

Figure.1. Values of and differences in ln HF (panel-a), ln LF (b), lnVLF (c), QTc (d), Tp-e (e), and Tp-e/QTc (f) in each stage, among mild to moderate and severe obstructive sleep apnea subjects and controls (three groups). Where, *p< 0.05: severe OSA vs. normal control.

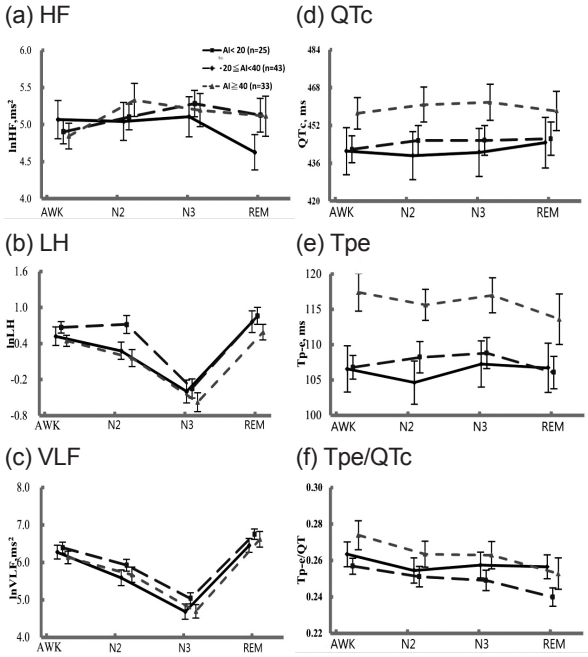

Figure.2. Values of and differences in ln HF (panel-a), ln LF (b), lnVLF (c), QTc (d), Tp-e (e), and Tp-e/QTc (f) om each stage, among mild, moderate, and high arousal subjects (three groups). Where, *p <0.05: high frequency of arousal vs. low frequency of arousal; # p <0.05: high frequency of arousal vs. moderate arousal.

provide supporting evidence for higher risk of nocturnal arrhythmia in subjects with severe OSA or restless sleep, but also for accumulated rather than real time impact of autonomic dysfunction underpinning elongated QTc and Tp-e periods. These findings infer that severe sleep apnea and/or repetitive night sleep arousals account for, at least in part, cardiac arrhythmia or sudden death around the clock.

Features that make the ECG indices QTc, Tp-e and Tp-e/QTc attractive for evaluating the likelihood of arrhythmia are ease of measurement, ease of interpretation, and noninvasiveness. In addition, they are almost instantaneous measures, requiring only a couple of minutes to reflect adaptability to sympathetic activity. Furthermore, with the need to compare current results with those of previous studies and a sole V2 ECG lead available, we included QTc, Tp-e interval and Tp-e/QTc in our calculations. According to a previous finding that there is a difference in QT dispersion between individuals with OSA (averaged AHI= 51.9)24 and healthy controls only during sleep, we investigated these ECG indices during night sleep, when extrinsic confounders are minimized. Due to the circadian effect, parasympathetic nerve activities lengthen QTc intervals during the dark period in common marmosets[25] and in normal subjects[17].Among normal controls[17] and OSA patients[26], QTc values were quite similar to those of previous studies (434 and 421-482 ms, respectively), suggesting that our data are reliable. In the current study, QTc >450ms was seen in <1/3 of normal controls, 1/2 of M- and ~2/3 of S-OSA subjects; and >500ms was seen in ~1/5 of S-OSA. However, there were no incidences of ventricular arrhythmia.

Several studies have shown that OSA increases risks of ventricular arrhythmia[27] and sudden cardiac death. However, other studies[28] have revealed conflicting results. For example, Dursunoglu et al.[15] and Nakamura et al.[24] observed that the QT interval is prolonged in OSA subjects. Baumert

et al.[29] indicated that OSA is associated with changes in QT interval variability. However, Barta et al.[30] did not find similar results. Furthermore, Kilicaslan et al.[31] reported that QT and QTc intervals do not differ between OSA patients and controls, but other indices of ventricular repolarization (namely Tp-e, Tp-e/QT ratio, and Tp-e/QTc ratio) increase. QTc was elongated in our subjects with severe OSA; whereas Tp-e interval, but not Tp-e/QTc, was prolonged in those with the largest number of arousals. These inconsistent results among studies might be due to the uneven effects of factors on these ECG indices, such as female proportion, body mass index, smoking habit, shift worker, hypertension, left ventricular hypertrophy and possibly race. Compared to their Western counterparts, our male subjects had high percentages of current smoking habit, lower BMI and sedentary lifestyle.

Changes in spectral measures over various ultradian stages in the current study were similar to the findings of our previous study[44] and another study[9]. While changes in indicators on HRV analysis reflect almost real-time autonomic effects on sinoatrial node of heart, the direct assessment of norepinephrine spillover is the gold standard for assessing cardiac sympathetic activity. By using this technique for patients with affective disorder, Baumert et al.[32] demonstrated a positive correlation between cardiac norepinephrine spillover and QTc interval only in subjects with spillover values within normal range. This finding was in line with another observation that QTc is prolonged by epinephrine infusion in healthy subjects. Conversely, investigating cardiac sympathetic function in patients with long QT by applying ^{123}I-metaiodobenzylguanidine (MIBG) single photon emission computed tomography, Kies et al.[33] observed a distinct regional pattern of impaired cardiac sympathetic function independent of QTc intervals (plus clinical expression and the underlying genotype). Present as a nonspecific secondary phenomenon instead of an underlying cause, these defects putatively indicate a higher risk for arrhythmogenesis. Taken together, the above data partially interpret why automatic nervous potentials were unrelated to QTc intervals, Tp-e and Tp-e/QTc ratio in the current study. The cardiac sympathetic activity in our severe OSA patients was likely due to "early phased or subclinical" long QT syndrome and our subjects with severe OSA or hyperarousal exhibited more vulnerability to ion channelopathy in their myocardium through long-term detrimental impact. Further studies are needed to verify these hypotheses.

The QT interval covers ventricular depolarization and repolarization, whereas the Tp-e interval is more representative of the period of transmural repolarization[34] or repolarization of the whole left ventricle[35]. Therefore, Tp-e measurement is one of the best methods for evaluating the dispersion of repolarization. Clinically, Tp-e prolongation indicates the period of vulnerability to ventricular reentrant, and may trigger life-threatening ventricular arrhythmias in patients with myocardial infarction, hypertrophic cardiomyopathy, or channelopathic heart disease.[13, 36] Interestingly, Cakici et al.[37] reported that one night of sleep deprivation is reflected in the prolonged period of ventricular repolarization in healthy young adults, in terms of ECG surrogates such as Tp-e interval, QT interval, Tpe/QT ratio and QT dispersion. They suggested that one night of sleep deprivation leads to subclinical left ventricular diastolic dysfunction. Our hyperarousal subjects potentially also suffered from severe OSA, superficial sleep, sleep desaturation, and high blood pressure in the morning. In addition to adverse OSA effects, our subjects presented with severe consequences of long-term sleep deprivation. With prolonged QTc or Tp-e, but similar Tp-e/QTc, our subjects with severe OSA or hyperarousal might have electric conduction delay in both depolarization and repolarization of ventricles. We thus speculated that insomnia patients with features of long sleep latency, repetitive arousals, and low sleep efficiency also have lagged ventricular repolarization. This can worsen in the presence of sleep apnea.

Limitations

The findings of this study should be cautiously applied to females, and other ethnicities. Clearly, OSA patients are not always obese in the Asian

population, which is quite different from Western populations. Moreover, female sex hormone levels might prolong QT interval.In addition, several limitations should be noted: 1) Bazett's formula[38] is inaccurate for calculating higher heart rate though no method is best. 2) Smokers[39] might have more prolonged QTc than nonsmokers. 3) Without serum electrolyte data, electrolyte disturbances such as hypokalemia, hypocalcaemia and hypomagnesaemia may have confounded our results. 4)Several metabolic factors[40-42] that might influence ventricular repolarization were not measured or calculated. 5) Sex hormone status[18] and echocardiography for atrial dilatation or ventricular hypertrophy were not measured or performed,[43] particularly in obese subjects.

Conclusions

Among our male workers, QTc or Tp-e prolongation with constant Tp-e/QTc was found in severe OSA or hyperarousal subjects in pre-sleep wakefulness and various sleep stages, which was not reflected in changes in corresponding HRV parameters. This suggests that long-term accumulation of adverse effects of OSA or arousals, rather than acute autonomic activities, play a role, at least in part, in the dysfunction of ventricular depolarization and/or repolarization, in turn leading to cardiac arrhythmia or sudden death around the clock.

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