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Influence of gender on the QT interval variability and duration in different wake–sleep stages in non-sleep apneic individuals: Analysis of polysomnographic recordings

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Abstract

Introduction: The aim of the study was to determine the influence of gender and sleep stages, especially rapid eye movement sleep (REM), on QT interval variability and duration in normal subjects.

Methods: Polysomnographic recordings of 24 male and 24 female patients without obstructive sleep apnea were analyzed. In each patient, the QT interval variability index (QTVI) and the corrected QT interval (QTc) values were calculated as means of 2 awake, 4 non-rapid eye movement sleep (NREM) and 3 REM episodes, 300 s each. For the QTc calculation, five different correction formulas were used.

Results: Gender-related differences in the QT interval variability and duration were detected between all sleep stages ($P < 0.05$). In males, mean values of QTVI while awake, in NREM and REM sleep were -1.1 ± 0.2, -1.1 ± 0.3, -1.3 ± 0.2. In females, mean values of QTVI were -0.9 ± 0.4, -0.9 ± 0.4, and -1.1 ± 0.3, respectively. No difference between sleep stages was detected in the mean values of QTVI and QTc in both groups ($P > 0.05$).

Conclusion: The results of our study demonstrate no significant overall impact of sleep stages on ventricular repolarization variability and duration during physiological sleep in both genders. We found gender differences in the mean values of QTVI and QTc during different sleep stages, which confirm that gender is a modulating factor of ventricular repolarization.

Keywords: QT interval variability index; Rate-corrected QT interval duration; Sleep stages; REM sleep

Introduction

During the last decades, obstructive sleep apnea (OSA) has been associated with the pathogenesis of major cardiovascular diseases, cardiac arrhythmias and sudden cardiac death (SCD) [1–5]. In breathing-related sleep disorders chronic sleep fragmentation and intermittent hypoxia may shift the sympatho-vagal balance toward sympathetic predominance and vagal withdrawal [6] which may predispose to increased myocardial electrical instability. It has been determined that the major subgroups susceptible to adverse influences of surges in sympathetic activity during rapid eye movement (REM) sleep are cardiac [7] and OSA patients [4]. However, the gender dependence of the magnitude and consequences of elevated sympathetic drive during sleep, particularly in REM sleep, are less known. Gender is an important modulating factor of ventricular repolarization, with females having longer action potentials [8], higher susceptibility to several arrhythmias and predisposition to arrhythmogenic effect of certain drugs than the same-aged males [9].

Non-invasive parameters such as elevated ventricular repolarization variability and prolongation have been recognized as powerful predictors of arrhythmic events and SCD in population with heart disease [1,10–13]. OSA-related arrhythmogenic risks have increasingly received attention by medical community, at the same time, only few studies have examined QT interval properties in OSA patients [14,15] and even more limited data [16] concerning the QT interval variability and changes in physiological sleep are available. Since REM sleep is characterized by sympathetic surges and elevated sympathetic tone influences both the QT interval variability and duration, the assessment of modulatory effects of various sleep

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stages on ventricular repolarization parameters in males and females may add more understanding to arrhythmia genesis in OSA patients. To our best knowledge, studies to compare QTVI and various QT interval correction formulas while awake, during non-rapid eye movement (NREM) and REM sleep stages between genders have not been published.

In the present study, we evaluated the gender difference of QT interval variability and duration in different sleep stages by analyzing polysomnographic recordings in normal non-apneic patients.

Methods

Study population

We initially examined the data of 176 (106 men, 73 women) patients from 20 to 80 years referred to the Mae Pindmaa Sleep Clinic (Tallinn, Estonia) between 2013 and 2014 for a polysomnography (PSG) investigation because of clinically suspected breathing-related sleep disorders. The data on the demographics, height, weight, coexisting conditions, and use of medications of each person were collected at the time of PSG. In this study, we first selected 94 (52 man and 42 women) patients without sleep apnea (apnea–hypopnea index <5). We then narrowed the sample by selecting only patients who had body mass index (BMI) ≤ 35 kg/m^2. Of the 88 (52 men and 36 women) remaining patients, 54 (30 men and 24 women) patients who exhibited normal ECG (sinus rhythm, QTc interval duration of <440 ms), had no other clinically significant comorbidities, and were not receiving medications known to affect the QT interval parameters (e.g. I and III class antiarrhythmic, antihistaminic, psychotropic, or antibiotic drugs) were targeted. In this study, male patients were matched by age with an equal number of female patients (24 male and 24 women). The flow diagram of the selection process is shown in Fig. 1.

The study was approved by the Tallinn Medical Research Ethics Committee at the National Institute for Health Development.

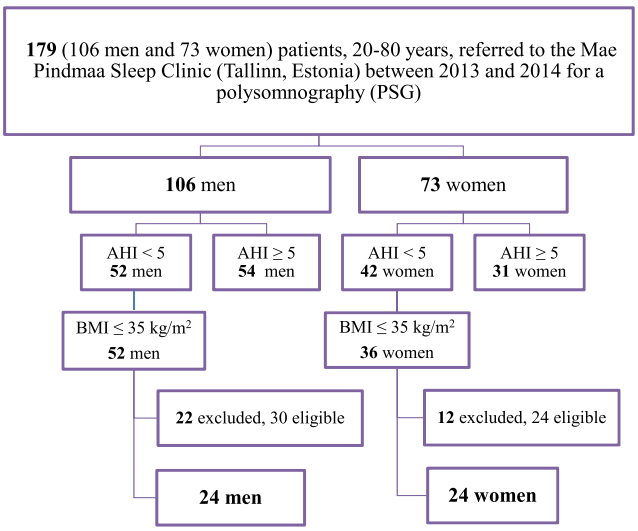

Fig. 1. illustrates the flow diagram of the study population selection process.

Polysomnographic recordings analysis

The PSG recordings were obtained using the polysomnography recorder Rembrandt Monet Artist SLP EZ 24 (Medicare Automation B.V, the Netherlands). In all patients the following signals were simultaneously recorded: electrocardiography, electro-oculography, electroencephalography, submental and anterior tibialis electromyography, arterial oxyhemoglobin saturation (SpO_2), oronasal air flow, thoracic and abdominal respiratory movements, snoring sound, and video monitoring. The duration of the recordings was from 8 to 9 h. The sampling frequency for the physiological signals was 200 Hz. Data processing was performed using the Rembrandt Analysis Manager (version 7.5, Medicare Automation B.V, the Netherlands). Sleep stages were confirmed visually using standardized procedures in accordance with the Technical Report of American Academy of Sleep Medicine published in 2007 [17] by a well-trained, certified, and experienced sleep technician. Recording segments presenting frequent artifacts were excluded from the analysis. In each patient, two awake, four NREM (stage II and III) and three REM sleep episodes (300 s each) suitable for processing were selected.

ECG analysis

The ECG lead II signals from the polysomnograms were anonymized and converted to EDF format. The signals were resampled to sampling frequency of 512 Hz and were pre-processed in LabVIEW (National Instruments, USA) environment, applying the signal converting Physionet toolkit. The R-wave peaks were detected and the extrasystoles identified using Pan-Tompkins algorithm implemented by P. S. Hamilton (Eplimited Ltd., USA). The RR intervals were converted to normal-to-normal intervals. Ectopic beats, as well as pre-and post-extrasystolic beats, were excluded from the analysis. The T-wave location and type were detected using Ecgpuwave software [18]. We measured the mean QT interval duration in all episodes. The T-wave apex and the T-wave end points detection were visually verified by an experienced investigator. Only monophasic well-defined T-waves were accepted. The end of T-wave was determined using the downslope tangent method described previously [19]. The QT variability and QTc analyses were performed for 5-min (300 s) ECG segments. For this analysis we chose two awake episodes (10 min in total), four NREM episodes (15 min stage II and 5 min stage III), and three REM episodes (15 min in total).

The QT variability index was evaluated by the Berger's formula [10], which quantifies the magnitude of the QT interval fluctuations, normalized by both the mean QT duration and the magnitude of heart rate fluctuations. The index is calculated for each subject as the logarithm of the ratio of normalized QT variance to heart rate variance: QTVI = log10 (QTv/QTm^2/RRv/RRm^2). In this formula, QTv represents the QT interval variance, QTm is the mean QT interval, RRv is the RR interval variance, and RRm is the mean RR interval. A single QTVI measurement during 256 s [10] is considered powerful enough to discriminate high-risk patients. To be even more precise, we assessed QTVI in two awake, four NREM and three REM episodes and presented the data as