Sex Differences in Nocturnal Ventricular Repolarization Variability

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Abstract

The objective of this study was to investigate sex differences in nocturnal repolarization variability. We analyzed polysomnographic recordings of 2,263 participants enrolled in the Sleep Heart Health Study. In addition to standard heart rate variability (HRV) parameters, we extracted beat-to-beat QT interval variability (QTV) parameters from consecutive epochs of 5 minutes by employing two-dimensional signal warping. We used a general linear mixed model (GLMM) to investigate the relationship between extracted parameters and sex under consideration of clinical and sleep characteristics. The GLMM shows a significant differences ($P < 0.001$) of sex on QTV, T wave amplitude and standard HRV parameters. In addition, the GLMM shows significant effects of sleep stages and age. While standard deviation of QT intervals is significantly higher in females than males ($P < 0.001$), T wave amplitude is about 30 % lower ($P < 0.001$) in females than in males. Applying T wave amplitude correction to QTV to minimize within-group variability and removed sex-related differences ($P = 0.581$). A demonstrated difference in uncorrected QTV is is likely due to lower T wave amplitudes in females. By applying a correction formula, we can account for T amplitude differences. Corrected QTV measures might yield improved characterization of autonomic nervous system activity during sleep.

1. Introduction

Sleep is known to modulate the activity of the autonomous nervous system and thereby heart rate variability (HRV) [1,2]. QT interval variability (QTV) is also affected by autonomous nervous system, but reports on its behavior during sleep are highly inconsistent [2–4]. Both, physiological and technical influence factors, might contribute to existing inconsistencies.

While many previous studies failed to prove an impact of sleep stages on ventricular repolarization variability [2, 3, 5], we recently demonstrated its existence [4]. QTV decreases from wakefulness to non-rapid eye movement (NREM) sleep and is increased in rapid eye movement (REM) sleep. Thus, QTV shows similar sleep stage characteristics as expected from HRV. In addition to the dependence on sleep stages, a significant influence of age, sex, apnea-hypopnea index, and T wave amplitude could be shown [4]. However, differences in T wave amplitude yield QTV differences [6, 7]. In this study we want to investigate in the relationship between nocturnal QTV and sex under consideration of sleep and T wave characteristics.

2. Material and Methods

2.1. Data Material

We used the data material originating from the Sleep Heart Health Study (SHHS) [8] provided by the National Sleep Research Resource (NSRR) [9]. SHHS is a prospective cohort study that was designed to investigate the relationship between sleep-disordered breathing and cardiovascular disease. Initially 6,441 participants were recruited in the first visit of SHHS during 1995 and 1998 from 9 existing prospective cohorts. During a second visit between 2001 and 2003 a second polysomnogram was obtained of 3,295 participants.

Because the ECG sampling rate of the first visit does not meet the requirements for QTV analysis [10], we used the recordings of the second visit. The NSRR database of SHHS visit 2 provides polysomnograms of 2,651 subjects (1,226 men, mean age 62.4 $\pm$ 10.5 years, age balanced to sex). Each polysomnogram was recorded in an unattended setting, usually in the homes of the participants, and contains full polysomnography, event scoring, and sleep staging. For further sleep stage analysis we combined sleep stages 3 and 4 to be consistent with the American Academy of Sleep Medicine standard [11]. The ECGs were recorded at bipolar lead II and mostly sampled at 250 Hz and processed with a 60 Hz notch filter. However, there are also

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few ECGs which were recorded at 256 Hz.

2.2. Feature Extraction and QTV Quantification

To extract RR intervals, QT intervals, and T wave amplitudes from ECG we used iterative two-dimensional signal warping (i2DSW) [12, 13]. The method is capable to account of subtle inhomogeneous shape variations of the ECG waveform. i2DSW automatically generates a template beat with common features of interest (e.g. the PQ, QRS or QT intervals or amplitude related information) based on ensemble averaging of appropriate beats. Templates underwent a manual review by an expert to be excluded from further analysis if necessary. To adapt the template, a 2D mesh of warping points is superimposed. By shifting warping points in x- and y-direction and minimizing the Euclidean distance between template and the beat under consideration, the optimal template adaptation is calculated. From the adapted template, changes in annotated features can be tracked from beat to beat.

We applied automatic beat rejection [12] to exclude noisy heart beats. RR filtering [14] was applied to remove abnormal RR intervals. ECG variables were calculated for consecutive 5-min epochs and assigned to the most prevalent sleep stage during that period (wakefulness, NREM2, NREM3, and REM). We excluded 5-min epochs with more than 10 % exclusion for heart beats or RR intervals from further analysis.

2,236 recordings with a total of 191,893 5-min epochs were included in our analysis. To quantify HRV and QTV we calculated standard deviations of RR and QT intervals (SDRR and SDQT). In addition, T wave amplitude-corrected SDQT (cSDQT) [7] was calculated to consider the inverse relationship between QTV and T wave amplitude [6] defined as follows:

$$cSDQT = SDQT \cdot 10^{\left[m_c \cdot \log_{10}\left(\frac{\hat{T}_{amp}}{\overline{T}_{amp}}\right)\right]}$$

where $m_c = 0.36ms/V$, the T wave amplitude normalization coefficient ($\hat{T}_{amp}$) = 300 μV, and $\overline{T}_{amp}$ is the median of the absolute T wave amplitude [7].

2.3. Statistical analysis

We used a generalized linear mixed model (GLMM) to account for the dependence structure within each patient. All 191,893 consecutive 5-min epochs are considered in GLMM. Observations within a cluster show the individual dependence between cardiovascular parameters (SDQT, SDRR, cSDQT, and mean T wave amplitude) and fixed effects (see Table 1). To analyze possible relations between sex and mean T wave amplitude or sleep stages we considered the interaction terms between them in the GLMM. Linear regression analysis was performed to prove the inverse relationship between QTV and T wave amplitude for men and women. To account for the differences between sleep stages and sex, one-way ANOVA with repeated measures (rmANOVA) and multiple comparisons was used. Comparisons between men and woman for all sleep stages were performed with unpaired Student's t-test.

Table 1. GLMM fixed factors of SHHS-2 participants showing the significant effect of sleep stage on SDQT, SDRR, cSDQT and mean T wave amplitude and no significant effect of sex difference on cSDQT.

	P Values			
	SDQT	SDRR	cSDQT	Mean T_{amp}
GLMM	<0.001	<0.001	<0.001	<0.001
Sex (men/woman)	<0.001	<0.001	0.378	<0.001
Age, yr	<0.001	<0.001	<0.001	<0.001
Body mass index, kg/m^2	0.122	0.892	0.925	0.060
Total sleep time, min	0.546	0.431	0.916	0.615
Time spend in bed	0.891	0.809	0.381	0.328
NREM1, %	0.202	0.482	0.364	0.921
NREM2, %	0.186	0.538	0.415	0.946
NREM3 and NREM4, %	0.172	0.694	0.388	0.964
REM, %	0.180	0.686	0.345	0.973
Apnea-hypopnea index (no/mild/moderate/severe)	<0.05	<0.001	<0.01	0.118
Mean O_2 saturation, %	0.206	<0.01	0.283	<0.05
Mean T wave amplitude, μV	<0.001	<0.01	<0.01	—
Sleep stage (wakefulness/NREM2/NREM3/REM)	<0.001	<0.001	<0.001	<0.001
Sex×Mean T_{amp}	<0.001	0.105	0.466	—
Sex×Sleep stage	0.071	<0.001	<0.001	<0.001

GLMM, generalized linear mixed model; SDQT, standard deviation of QT intervals; SDRR, standard deviation of RR intervals; cSDQT, T wave amplitude-corrected standard deviation of QT intervals; T_{amp}, mean T wave amplitude; NREM, non-rapid eye movement; REM, rapid eye movement.

3. Results and Discussion

Table 1 shows the results of GLMM fixed effects for SDQT, SDRR, cSDQT and mean T wave amplitude. GLMM shows significant impact ($P < 0.001$) of sleep stage on all of them. Whereas SDQT, SDRR and mean T wave amplitude show significant effects ($P < 0.001$) to sex, cSDQT does not show this behavior ($P = 0.378$). Significant interaction ($P < 0.001$) between sex and mean T wave amplitude is only shown on SDQT and confirms the the impact of T wave amplitude to QTV. T wave amplitude correction removed sex-related effects and interaction between sex and T wave amplitude ($P = 0.466$) in cSDQT. Significant interaction between sex and sleep stages ($P < 0.001$) was evident in SDRR and cSDQT.

Figure 1 shows the linear inverse relationship between

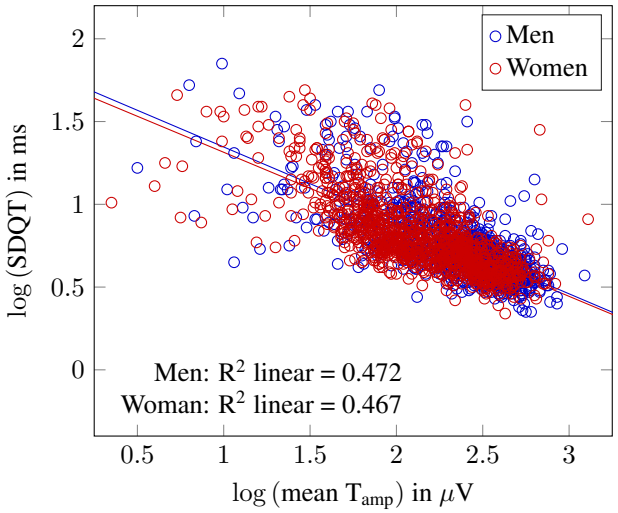

Figure 1. Linear regression analysis between logarithmized SDQT and logarithmized mean T wave amplitude for men and women. SDQT, standard deviation of QT intervals, ; T_{amp}, mean T wave amplitude; R^2, coefficient of determination.

QTV and T wave amplitude for men and women. Significant correlation between logarithmized SDQT and logarithmized mean T wave amplitude (coefficient of determination R^2 = 0.47, $P < 0.001$) for men and women were observed. The regression slope is similar for men and woman (both -0.44 $ms/\mu V$) but lower than previously reported for healthy subjects (-0.36 $ms/\mu V$) [7] which could be due to altered physiological and pathophysiological behaviors in patients with sleep disorders [2, 4].

One-way rmANOVA was used to analyze the relationship between cardiovascular parameters (SDQT, SDRR, cSDQT, and mean T wave amplitude) and sleep stages under consideration of sex. The effect of sleep stage was significant ($P < 0.001$) for all cardiovascular parameters. There was a significant effect ($P < 0.001$) of sex for SDQT, SDRR and mean T wave amplitude but not for cSDQT ($P = 0,976$). Figure 2 shows the characteristics of SDQT, SDRR, cSDQT and mean T wave amplitude to sleep stage according to sex. SDQT, SDRR and cSDQT decreased from wakefulness to NREM3 sleep for both men and women. In REM sleep, SDQT, SDRR and cSDQT were above the level of NREM. Mean T wave amplitude decreases while getting into deep sleep (NREM3) and is lower in REM compared to wakefulness. The behavior to sleep stages is similar for men and woman but absolute values differ for SDQT, SDRR and mean T wave amplitude. Post-hoc tests show that SDQT is significantly ($P < 0.001$) higher in woman (8.2 ± 6.7 ms) than men (7.1 ± 6.3 ms), whereas T wave amplitude is about 30 % lower ($P < 0.001$, 188.7 μV vs. 271.4 μV averaged for

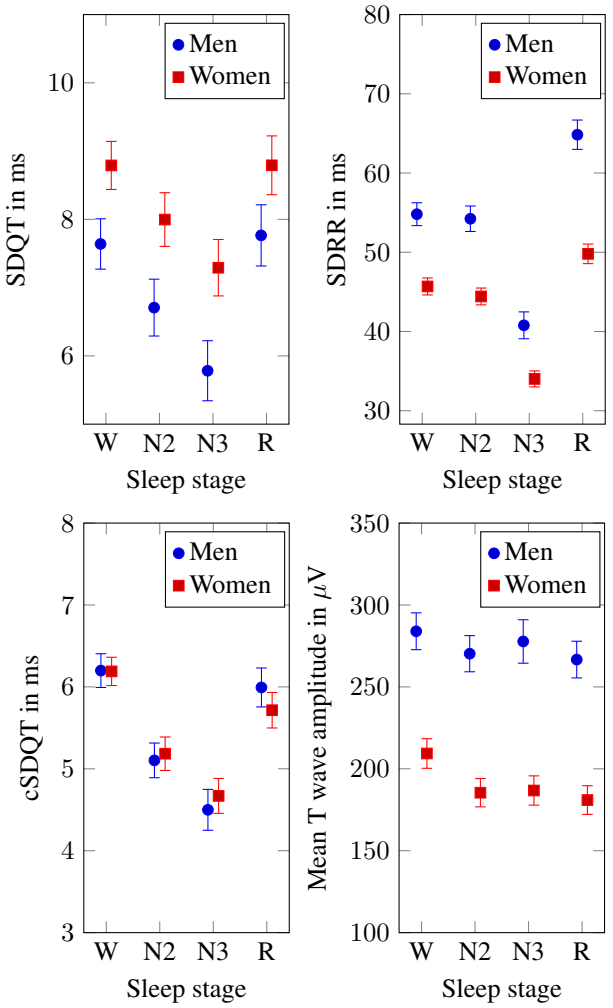

Figure 2. Average standard deviation of QT intervals (SDQT), standard deviation of RR intervals (SDRR), T wave amplitude-corrected standard deviation of QT intervals (cSDQT) and mean T wave amplitude characteristics according to sleep stage and sex (error bars: 1.96 · SE). Sleep stages were as follows: wakefulness (W), non-rapid eye movement stage 2 (N2), non-rapid eye movement stage 3 (N3), and rapid eye movement (R).

sleep stage). By T wave amplitude correction of SDQT there is no longer a significant difference ($P = 0.581$) between men (5.5 ± 3.1 ms) and women (5.4 ± 3.2 ms).

Our results confirm previous findings that sex differences affect the myocardial repolarization. Women have longer action potentials [1], reflected as longer QT intervals. Multiple statistical analyses show that sex differences in QTV are primarily a result of the T wave difference. We found similar characteristics of QTV and T wave amplitude according to sleep stages for men and women. By correcting for the T wave amplitude, corrected QTV mea-

surements become comparable between both.

4. Conclusion

We found a significant sex difference in nocturnal QTV. This difference is likely due to lower T wave amplitudes in females. By applying a correction formula, we can account for T amplitude differences. Corrected QTV measures show similar sleep stage characteristics for men and women and might yield improved characterization of autonomic nervous system activity during sleep.

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