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A new tool for QT interval analysis during sleep in healthy and obstructive sleep apnea subjects: a study on women

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Abstract: By monitoring the Q wave/T wave (QT) interval computed from electrocardiography (ECG) signals during sleep, it is possible to create a link between the ventricular repolarization and sleep stages. In this study, we aimed to find a robust and simple approach to automatically determine the fiducials on each 30-s sleep epoch, such as the Q, R, and T-end points, on long sleep ECG recordings in order to statistically analyze the effect of obstructive sleep apnea (OSA) and sleep stages on QT intervals. This is a retrospective study in which the ECG data extracted from the polysomnography recordings of 7 healthy women and 5 women with OSA, acquired in a sleep laboratory, were used. Experts annotated the sleep stage and OSA presence information for each 30-s epoch. Later, we visually selected epochs with clean signals from a total of 8324 epochs. On the selected epochs, we determined R peaks on each heartbeat, and by aligning each ECG portion corresponding to a heartbeat using those R points, we computed an average ECG signal for each epoch. On the average ECG signals, we developed a novel approach to find the Q and T-end points. With the help of Bazzet's formula, we computed the corrected QT interval (QTc) values for each epoch using the QT and the median RR interval. Finally, we analyzed the QTc values for the different sleep stages and healthy or OSA groups. We employed statistical approaches such as the Mann–Whitney U test, Freidman's test, and the Wilcoxon signed-rank test. As a result of this study, we found that OSA has a prolongation effect on the total duration of the ventricular depolarization and repolarization. We also observed that the QTc values computed in each sleep stage were significantly different between the healthy and OSA groups. Additionally, we discovered that within the healthy group, the QTc values were distinctive in the different sleep stages.

Key words: Sleep, ECG, QT interval, obstructive sleep apnea

1. Introduction

Polysomnography (PSG) is usually performed at night in sleep laboratories, and it is used to monitor various physiological processes that take place in the brain, eyes, skeletal muscles, lungs, and heart during sleep by connecting special electrodes and sensors to the associated locations on the body. To evaluate heart functions during sleep, electrocardiography (ECG) is employed. In such evaluations, ECG generally helps to observe the heart rhythm throughout the subject's sleep and investigate the potential for ventricular rhythm disturbances (arrhythmias). Specifically, abnormalities of ventricular repolarization are linked to life-threatening ventricular arrhythmias [1]. A parameter derived from the ECG signals called the Q wave/T wave (QT) interval can be used in the evaluation of repolarization abnormalities. The QT interval is calculated as the time duration between

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the beginning of the QRS complex and the end of the T-wave, and it reflects the electrical depolarization and repolarization of the ventricles. By monitoring the QT interval during sleep, it is possible to create a link between the ventricular repolarization and sleep stages. Many groups have reported their approaches, results, and assessments about the effects of sleep disorders and their treatments [2–4], panic disorder [5], sleep position [6], menopause and hormone replacement [7], caffeine intake [8], and drug intake [9,10] on the QT interval. Specifically, the variations of the QT interval related to sleep disorders such as obstructive sleep apnea (OSA) have been investigated in the last 20 years [2,3,11]. OSA is a complete or near complete cessation of airflow due to the obstruction of the upper airway for at least 10 s. Although it is a respiratory event, it affects the cardiovascular system. Therefore, the QT interval provides valuable information about apneic events [12]. In addition, there are studies focusing on the effect of the sleep stage on the QT interval [7,11,13,14]. In both OSA and sleep stage studies for the calculation of the QT intervals, researchers tend to select certain parts of the ECG traces in different stages, before and after the apneic events, and perform manual calculations on short recordings. They claim that these representative samples can be used for the analysis of the whole night. There have also been several automated QT interval measurement software programs developed by companies and researchers around the world [15–18] that attempt to analyze this parameter on every heartbeat. However, most of these software programs are not optimized for sleep studies.

In this study, we aimed to find a robust approach to automatically determine the fiducials on each 30-s sleep epoch, such as the Q, R, and T-end points, on long sleep ECG recordings in order to statistically analyze the effect of OSA and the sleep stages on the QT intervals. The RR intervals were also computed in order to correct the QT interval values for the heart rate. This new parameter is called the corrected QT interval (QTc) and it is the main focus of our analysis. In order to demonstrate the effectiveness of our approach, we performed a QTc analysis on 7 healthy women and 5 women with OSA.

2. Materials and methods

2.1. Subjects and measurements

This is a retrospective study in which the PSG data of 12 female subjects were used. The PSG data were acquired as part of routine diagnosis and treatment performed at Gülhane Military Medical Academy, Psychiatry Clinic Sleep Laboratories, Ankara, Turkey, and, thus, we did not need an ethics committee's approval. The data obtained to monitor the physiological parameters came from 32 channels of the PSG device (Somno Star Alpha Series 4, Sensor Media Corporation, Yorba Linda, CA, USA) in the laboratory. The electroencephalography, electrooculography, electromyography, ECG, and signals from the oronasal respiration, thoracic and abdominal movement, and oxygen saturation were recorded. The data were examined by sleep experts and manually scored for the sleep stage determination and OSA presence. They annotated each 30-s epoch as 1 of the 4 nonrapid eye movement (NREM) stages, wake, or rapid eye movement (REM) stage according to the Rechtschaffen and Kales scoring system [19]. As the sleep stages we combined NREM 3 and 4 and treated NREM 3 in accordance with a technical report of American Academy of Sleep Medicine published in 2007 [20].

By convention, lead II of the ECG was chosen to measure the QT interval. The sampling rate for the ECG measurement was 200 Hz, and the band-pass edge frequencies were 0.5 Hz and 40 Hz.

Table 1 describes the 12-subject study population. None of the patients had any kind of reported heart diseases. In addition to Table 1, we should note that in an average of 10.7% (range: 4.8% to 20.1%) of the epochs, an apneic event occurred in the OSA group, and the percentage of epochs with apnea varied from 4.8% to 20.1%. The average apnea/hypopnea index for the OSA group was 19.5 (ranging from 12 to 31).

Table 1. Summary of the study population. The values in parentheses indicate the range. N is the number of subjects included in the study. OSA: obstructive sleep apnea.

	N	Average age (years)	Average sleep duration
OSA	5	55.4 (47–67)	6.9 (6.2–7.3) h
Healthy	7	27.9 (25–34)	7.0 (5.4–8.4) h

2.2. Data preprocessing

Single-channel ECG data coming from the PSG device were first converted into vector format to perform further processing and analysis using MATLAB (MathWorks Inc., Natick, MA, USA). In addition, the sleep stage and OSA presence information annotated for each 30-s epoch was transferred into MATLAB. We then created a graphical user interface in order to visually select the epochs with clean signals (i.e. leaving out the noisy or arrhythmic signals) from the dataset. In this step, we marked the selected epochs for their usage in the analysis part of this study. Figure 1 shows 2 examples of the ECG signals coming from a clean (left panel) and noisy (right panel) epoch. In around 5% of the epochs, the data were noisy or arrhythmic. A total of 8324 epochs were analyzed individually.

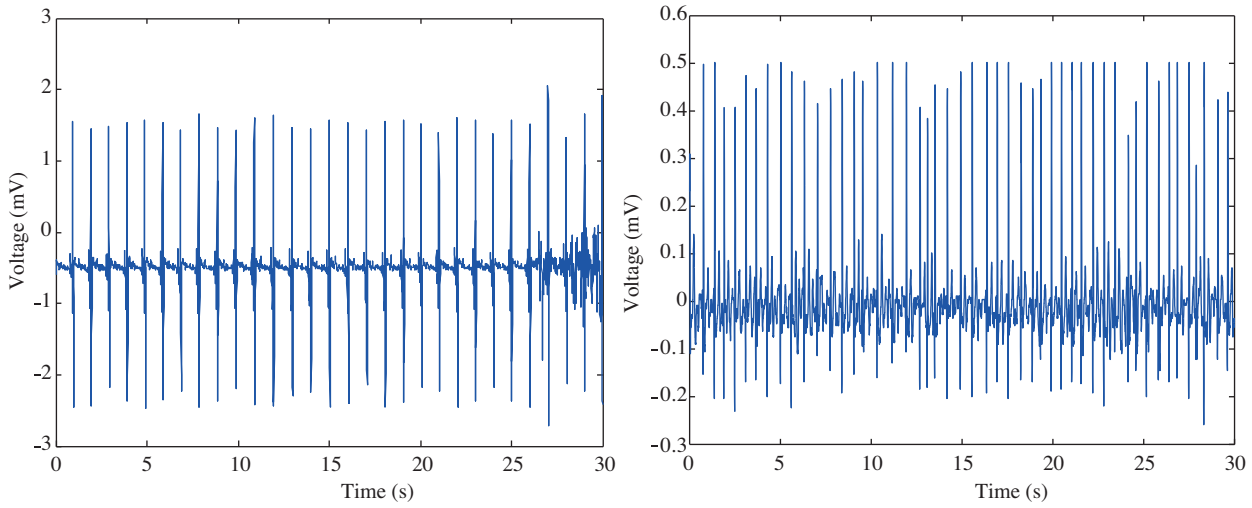

Figure 1. Two examples of the ECG signals coming from different epochs: a) a noisy epoch and b) a clean epoch.

2.3. RR interval computation

Once we selected the clean epochs for further processing, the R peaks of the heartbeats from each epoch were detected. In the R peak detection, we used a previously developed algorithm [21], in which a band-pass filter was first applied to the ECG signals for noise attenuation while preserving the necessary spectral content. The cutoff frequencies of the band-pass filter that we used were 0.5 and 40 Hz. The filter was based on the fast Fourier transform of the ECG signal. The unwanted frequency content was left out of the transform before the application of the inverse transform to obtain the filtered signal. The detection of the R peak was performed with an indicator, which takes the amplitude and the curvature of the ECG signal into account for distinguishing the R waves from the other waves. Using the R peaks that were found, we determined the RR intervals between the subsequent heartbeats. Later, we computed the median value of the RR intervals in order to use one value for each epoch.

2.4. Average heartbeat signal

In this study, instead of computing the QT intervals of each heartbeat, we preferred to determine one QT interval from each epoch, using the average QRST portion. In order to do this, we computed an average ECG signal representing one heartbeat (P-wave, QRS complex, and T-wave as a whole). Figure 2 depicts 2 average heartbeat signals from 2 different epochs. On the average ECG signal, we determined the Q and T-end points to compute a QT interval of each epoch. For the computation of the average ECG signal, we aligned each beat using their R peaks. On the first beat, the points located at 250 ms before and 550 ms after the R peak of that beat were assigned as the starting and end points of the signal to be used in the averaging process. The same approach was applied for the other beats on one epoch. These selected portions were aligned in that manner, and were summed and divided by the number of beats used in the summation. Therefore, an average ECG signal representing one heartbeat for each epoch was computed. This procedure was repeated for all clean epochs. We should also note that the average signal was very useful in double-checking the epoch's status as clean or noisy, because the average signal was distorted when the ECG was noisy in that specific epoch. Instead of displaying all of the heartbeats in an epoch, it is much easier to observe whether this epoch is clean or noisy on the average signal.

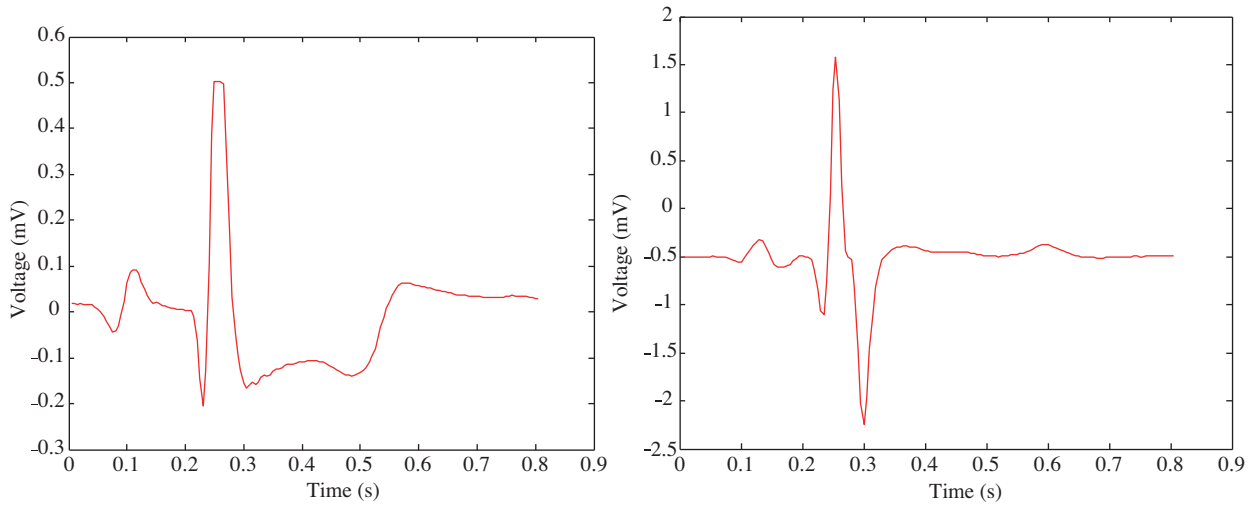

Figure 2. Two average heartbeat signals from different epochs.

2.5. QT determination using an average ECG signal

By consulting cardiologists and referring to the literature, we first defined the Q point as the initial downward (negative) deflection in the QRS complex and the T-end point as the end of the deflection that follows the QRS complex. As we have a clean signal and clear definitions, it seems to be an easy task to develop an algorithm for an automatic detection. However, almost every subject has a unique ECG pattern. Developing an algorithm that works on all types of ECG patterns is a hard task. The most crucial problem in finding the Q and T-end points on each average heartbeat signal from different patients is that their location on each patient's ECG is different from each other, which leads to incorrect QT durations. However, ECG recordings from the same patient do not alter suddenly, but rather gradually. We have selected the Q and T-peak points from one of the first epochs by clicking on the corresponding timing on the average heartbeat signal (using the MATLAB built-in function "ginput"). For finding the Q and T-end points automatically after marking the Q and T-peak points in one of the first epochs, we determined a window in which we performed the search. The algorithm

for finding the Q point is as follows: the Q point is usually the starting point of the deflection that occurs due to the atrial repolarization. However, in some beats, this deflection cannot be observed. In such cases, the Q point is the starting point of the complex that occurs due to the ventricular contraction. In both cases, the absolute voltage difference between the Q point and the subsequent point was larger than the difference between the preceding points (the slope of the line before the Q point should be close to 0) and less than the absolute difference between the following subsequent points that occur due to the sharp decrease or increase in the QRS complex. The window started at 50 ms (10 samples) before and ended at 25 ms (5 samples) after the marked Q point in each epoch. If the absolute difference between a point with its subsequent point was in the range of 0.0050–0.01 mV, then this point was assigned as the Q point. These voltages were determined by experimenting with different values. If there were multiple points, we selected the first one.

The algorithm for finding the T-end point is as follows: the T-end point is the end of the T-wave, where the voltage values come back to an isoelectric line after the deflection of the T-wave. To find the T-end point, we first found the T-peak point (the highest absolute voltage value in the T-wave) and computed the absolute difference between 1 subsequent point and the following 4 points. We performed this computation on 4 points in order to neglect the short pseudoisoelectric line that occurs in the biphasic T-waves. If all of the absolute difference values between a point and the following 4 points were less than 0.0029 mV, then that point was assigned as the T-end point. If there were more than one of these points, the one closest to the T-peak point was chosen. The length of the window after the T-peak was 80 ms (16 samples).

Figure 3 shows the marking of the computed Q, R, and T-end points as blue dots on an exemplary average heartbeat signal. For each clean epoch, we visually double-checked the locations of these points.

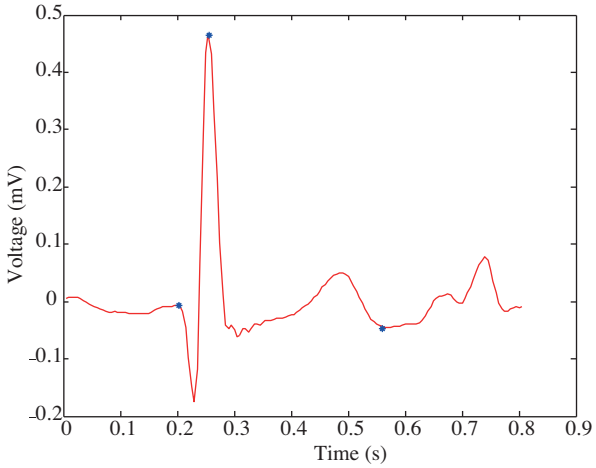

Figure 3. The computed Q, R, and T-end points are marked as blue dots on an exemplary average heartbeat signal.

2.6. QT correction

For each clean epoch, using the average ECG signal, we determined the Q and T-end points and computed the QT interval. We also computed the median of the RR intervals (as mentioned above), and thus we were able to correct the QT interval with the median of the RR intervals using Bazzet's formula (corrected QT or QTc) for each epoch [22].

2.7. Statistical analysis

Once we finished computing the QTc values for each clean epoch of each subject, we analyzed the QTc changes by asking the following questions: 1) Are the QTc value distributions from the 7 healthy women in 1 sleep stage different from those obtained from the 5 women with OSA in the same sleep stage? 2) Are the QTc value distributions coming from different sleep stages in a group (healthy or OSA groups) different from each other? 3) If they are different in general, which sleep stages are they pairwise different?

In order to search for the answers to these questions, we performed statistical comparisons of the QTc values obtained from the sleep stages, i.e. wake, NREM 2, NREM 3, and REM. We excluded NREM 1 from our analysis because the number of epochs was not enough for a proper comparison. The statistical methods employed were the Mann–Whitney U test, Freidman's test, and the Wilcoxon signed-rank test [23]. The Mann–Whitney U test is a nonparametric test (distribution-free) that is used to compare 2 independent groups of sampled data. Unlike the parametric t-test, this nonparametric test makes no assumptions about the distribution of the data (e.g., normality). We used this test method for the comparison of the QTc distributions between the healthy subjects and the subjects with OSA for each sleep stage. Freidman's test is also a nonparametric test used to compare observations repeated on the same group. This test is an alternative to the repeated measures ANOVA when the assumption of normality or equality of variance is not met. In this study, Friedman's test was useful in determining whether the QTc distributions between the different sleep stages in the same group were significantly different from each other. The Wilcoxon signed-rank test uses paired samples and is the nonparametric analogue of the dependent t-test for paired samples. This test uses 2 samples, but it is necessary that they should be paired. Paired samples imply that each individual observation of one sample has a unique corresponding member in the other sample. In our case, when Friedman's test yielded a significantly different distribution between the sleep stages, the Wilcoxon signed-rank test worked as a tool for pairwise comparison of the stages. We note that all of these tests use the ranks of the data rather than their raw values to calculate the statistic.

3. Results

Table 2 shows the summarized statistics of the median QTc values of each epoch, computed in an offline fashion for the ECG data acquired during a night sleep of the women in good health (healthy group) and of the women with OSA (OSA group). The mean, standard deviation, median, minimum, and maximum QTc values of NREM 2, NREM 3, REM, and the wake stages individually for each group are depicted in Table 2. The summarized statistics indicate that all of the statistical parameters of the QTc values computed from the OSA group were always greater than those of the healthy group. This observation demonstrates that OSA affects the total duration of the ventricular depolarization and repolarization in a negative way. Such an increase might cause a significant vulnerability to lethal cardiac arrhythmias during a night of sleep. It is worth pointing out that the standard deviation values in the OSA patients were greater than those of the healthy subjects, which might mean that there is increased intrastage variability in the QTc values. We also note that in the healthy subjects, as the depth of the sleep increased, the QTc increased accordingly.

Using the Mann–Whitney U test, we performed a comparative study on the QTc distributions between the healthy subjects and the subjects with OSA in the same sleep stage. In Table 3, the results of this part of our statistical analysis are given. In general, the results show that QTc values were different in the wake, NREM 2, NREM 3, and REM stages between the healthy and OSA groups, while all of the corresponding 2-tailed asymptotic significance values were less than 0.05. This result was also in parallel with the statistics

shown in Table 2. What we can deduce from the results summarized in Table 3 is that the corrected QT interval values were different in the healthy women than those in the women with OSA. The difference between the sleep stages was obvious.

Table 2. Statistical summary of the QTc values for the different sleep stages and groups.

Group		N	Mean	Std. Dev.	Median	Min.	Max.
NREM 2	Healthy	7	420.4	9.1	422.2	400.6	428.2
	OSA	5	467.2	23.2	475.4	442.5	493.3
NREM 3	Healthy	7	423.2	11.1	428.3	400.3	431.9
	OSA	5	470.2	13.6	475.6	453.7	484.9
REM	Healthy	7	415.5	9.6	417.9	397.6	425.6
	OSA	4	458.8	21.1	458.0	437.6	481.8
Wake	Healthy	7	408.9	10.6	409.4	393.5	422.1
	OSA	5	466.8	19.4	466.9	440.4	494.5

Table 3. The results of statistical comparisons using the Mann–Whitney U test. Asymp. Sig. (2-tailed) corresponds to 2-tailed asymptotic significance values.

Group	Mann-Whitney U	Wilcoxon W	Z	Asymp. Sig. (2-tailed)
NREM 2	0.00	28.00	–2.84	0.004
NREM 3	0.00	28.00	–2.84	0.004
REM	0.00	28.00	–2.65	0.008
Wake	0.00	28.00	–2.84	0.004

In the second statistical analysis, according to Freidman's test as shown in Table 4, we found that the QTc medians were different in the different sleep stages within the healthy group; however, this was not the case for the OSA group. This result indicates that in women with OSA, the difference between the sleep stages in terms of the total duration of the ventricular depolarization–repolarization activity becomes insignificant. Another observation is that the QTc might be used as a parameter to differentiate between the sleep stages for long PSG recordings.

Table 4. The results of the statistical comparisons using Friedman's test.

Group	N	Chi-square	Asymp. Sig. (2-tailed)
Healthy	7	14.74	0.002
OSA	4	2.10	0.552

Finally, according to the Wilcoxon signed-rank test, whose results are summarized in Table 5, the comparison of the QTc medians within the healthy group for the different sleep stages, such as REM-NREM 2, wake-NREM 2, REM-NREM 3, and wake-NREM 3, demonstrated a significant difference between each other. In the healthy women, we found that the difference between NREM 3 and NREM 2 and between wake and REM were not significant. For each pairwise comparison, the Z values and 2-tailed asymptotic significance values are given in Table 5.

Table 5. The results of the statistical comparisons using the Wilcoxon signed-rank test.

Group		Z	Asymp. Sig. (2-tailed)
Healthy	NREM3 - NREM2	–1.690[a]	0.091
	REM - NREM2	–2.201[b]	0.028
	Wake - NREM2	–2.197[b]	0.028
	REM - NREM3	–2.366[b]	0.018
	Wake - NREM3	–2.366[b]	0.018
	Wake - REM	–1.352[b]	0.176

[a] based on negative ranks, [b] based on positive ranks.

4. Discussion

The analysis of cardiac activity during sleep is a topic of interest for researchers around the world. Specifically, the heart rate and ventricular repolarization dynamics during the different sleep stages are studied under various disease conditions or in healthy subjects [12,13]. In a previous study, a group (one of the authors of this manuscript, BY, was the principal investigator in that group) studied the variation of the RR interval in different sleep stages [11]. They proposed the use of the RR-derived parameters to classify the sleep stages in healthy individuals and OSA patients for continuous monitoring of the night's sleep. The determination of the R peaks on the QRS complexes and the computation of the RR intervals in each 30-s epoch were relatively easy. In that study, they investigated the computing of the QT intervals on each heartbeat using different approaches. These approaches failed at that time and, therefore, the results were not published. The computation of the QT intervals during sleep and the analysis of the dynamics/variations of the corrected QT intervals for the different sleep stages is necessary for gaining a deeper insight into this topic. After the publication of that manuscript, we started new research on finding a relatively more clever approach in the computation of the QT intervals on a similar dataset. Once the algorithm was developed and tested under various ECG morphologies, we wanted to compare the QT intervals between the different sleep stages of healthy and apneic subjects using statistical methods such as the Mann–Whitney U, Friedman, and Wilcoxon signed-rank tests.

Specifically, in the first part of this study, we aimed at developing a novel approach in determining the QT intervals. Here, we did not prefer to compute the QT intervals of each heartbeat and then select one or several parameters (for example, mean or median) for each epoch. We thought that it was logical to assume small variations in the ECG signals in one epoch. Therefore, we proposed that first finding the R peaks and aligning the ECG portions corresponding to each heartbeat using those R-peaks could be used in the computation of an average heartbeat signal (P-wave, QRS complex, and T-wave as a whole) as the representative of that epoch. Furthermore, we developed a semiautomatic approach for finding the Q and T-end points on that average signal. Consequently, we obtained the QTc for all manually selected clean epochs. Later, using the statistical analysis tools, we performed a comparison of the QTc values for answering certain questions that were posed before the onset of this study. We first found that OSA negatively affects the total duration of the ventricular depolarization and repolarization, which might cause a significant susceptibility to deadly arrhythmias during sleep. We also observed that the QTc values computed in each sleep stage were significantly different between the healthy and OSA groups. Additionally, we discovered that within the healthy group, the QTc values were distinctive in the different sleep stages, which was not true for the OSA group. Here we note that, in women, OSA causes an insignificant variance between the sleep stages in terms of the ventricular depolarization–repolarization duration. In contrast, in healthy subjects, the QTc values increased from wake to REM and to NREM 2 and 3. Finally,

we determined that, in healthy women, the pairwise comparisons of the QTc distributions other than NREM 2 and NREM 3, and the wake and REM stages, were significantly different from each other.

In this study, our first aim was to develop an easy approach for continuous QTc computation on nightlong ECG signals. Many studies have used representative epochs or selected data (not the data coming from the whole night) or commercial software for analyzing certain cardiac dynamics during sleep [1,2]. We think that averaging-based QT interval determination would be a promising alternative for researchers working in this field. This approach can easily be employed in MATLAB and thus does not require commercial software. We note that averaging of the ECG data of an epoch might be used in determining whether it is noisy or clean for further statistical analysis.

Our second aim was to present a showcase in the analysis of the QTc interval data coming from healthy and diseased individuals in terms of the sleep stages. For investigations on the effects of sleep disorders and their treatments, the psychological status, drug or substance intake, cardiac problems, etc. on the QT interval, such an approach might be useful and simply modifiable for custom study and analysis designs.

One of the limitations in our study was that we used a relatively small number of patients for the QT analysis. Extrapolation of our findings would require confirmation in a broader patient sample. In addition, the QT analysis requires ECG recordings of reasonable quality. We have selected epochs with clean ECG signals manually; however, it is not a difficult task to implement an automatic approach to exclude epochs with ectopic beats and artifacts.

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