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Nocturnal ventricular repolarization lability predicts cardiovascular mortality in the Sleep Heart Health Study

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Schmidt M, Baumert M, Penzel T, Malberg H, Zaunseder S. Nocturnal ventricular repolarization lability predicts cardiovascular mortality in the Sleep Heart Health Study. *Am J Physiol Heart Circ Physiol* 316: H495–H505, 2019. First published December 14, 2018; doi:10.1152/ajpheart.00649.2018.—The objective of the present study was to quantify repolarization lability and its association with sex, sleep stage, and cardiovascular mortality. We analyzed polysomnographic recordings of 2,263 participants enrolled in the Sleep Heart Health Study (SHHS-2). Beat-to-beat QT interval variability (QTV) was quantified for consecutive epochs of 5 min according to the dominant sleep stage [wakefulness, nonrapid eye movement stage 2 (NREM2), nonrapid eye movement stage 3 (NREM3), and rapid eye movement (REM)]. To explore the effect of sleep stage and apnea-hypopnea index (AHI) on QT interval parameters, we used a general linear mixed model and mixed ANOVA. The Cox proportional hazards model was used for cardiovascular disease (CVD) death prediction. Sex-related differences in T wave amplitude ($P < 0.001$) resulted in artificial QTV differences. Hence, we corrected QTV parameters by T wave amplitude for further analysis. Sleep stages showed a significant effect ($P < 0.001$) on QTV. QTV was decreased in deep sleep compared with wakefulness, was higher in REM than in NREM, and showed a distinct relation to AHI in all sleep stages. The T wave amplitude-corrected QTV index (cQTVi) in REM sleep was predictive of CVD death (hazard ratio: 2.067, 95% confidence interval: 1.105–3.867, $P < 0.05$) in a proportional hazards model. We demonstrated a significant impact of sleep stages on ventricular repolarization variability. Sex differences in QTV are due to differences in T wave amplitude, which should be corrected for. Independent characteristics of QTV measures to sleep stages and AHI showed different behaviors of heart rate variability and QTV expressed as cQTVi. cQTVi during REM sleep predicts CVD death.

NEW & NOTEWORTHY We demonstrate here, for the first time, a significant impact of sleep stages on ventricular repolarization variability, quantified as QT interval variability (QTV). We showed that QTV is increased in rapid eye movement sleep, reflective of high sympathetic drive, and predicts death from cardiovascular disease. Sex-related differences in QTV are shown to be owing to differences in T wave amplitude, which should be corrected for.

cardiovascular death; electrocardiogram; QT interval variability; sex; sleep

INTRODUCTION

Acute cardiovascular events are known to exhibit circadian patterns with fewer events at night compared with the morning hours (11, 26). This nocturnal decrease has been related to nocturnal physiological quiescence and is nonuniformly distributed across sleep (23). Sleep stage-dependent fluctuations in autonomic nervous system activity (ANS) and circulating catecholamines appear to play a key role in this interaction. Higher sympathetic activity during rapid eye movement (REM) sleep compared with nonrapid eye movement (NREM) sleep has been proposed as a possible mechanism causing nocturnal arrhythmias (43).

Sleep state dependence of ventricular repolarization lability may trigger malignant cardiovascular events (25) and could provide informative risk stratification protocols. Beat-to-beat QT interval variability (QTV) captures ventricular repolarization lability (2, 7) and is a predictive of cardiovascular mortality (2, 7, 29). QTV shows increased diurnal variation in in the morning (14, 41) and in patients with heart failure and documented ventricular tachycardias (15). Sympathetic tonus modulates ventricular repolarization in the healthy myocardium, but its effect on diseased cardiac substrate is less clear (16, 27, 35). Sympathetic tone is higher in REM sleep than in NREM sleep (40), but, surprisingly, previous studies have reported no sleep stage-specific changes in QTV (4, 22, 44, 45). This fact seems all the more puzzling because heart rate variability (HRV) that influences over QTV reflects such changes (4, 8, 42). Some works on QTV during sleep indicate possible limitations of their studies (44, 45), e.g., used QT interval algorithm (5, 37), the inverse relationship between QTV and T wave amplitude (20, 36), and the size of the study population. All such factors are likely to affect QTV results (44, 45). In addition, QTV measures that include the influence of HRV, which is largely under vagal control, are less conclusive (31).

The presented study was conducted to *1*) quantify nocturnal ventricular repolarization lability according to sleep stages in a large population cohort and *2*) investigate its association with cardiovascular mortality.

METHODS

Data material. The used data material originate from the Sleep Heart Health Study (SHHS) (32), a prospective cohort study that was designed to investigate the relationship between sleep-disordered breathing and cardiovascular disease (CVD). Briefly, 6,441 partici-

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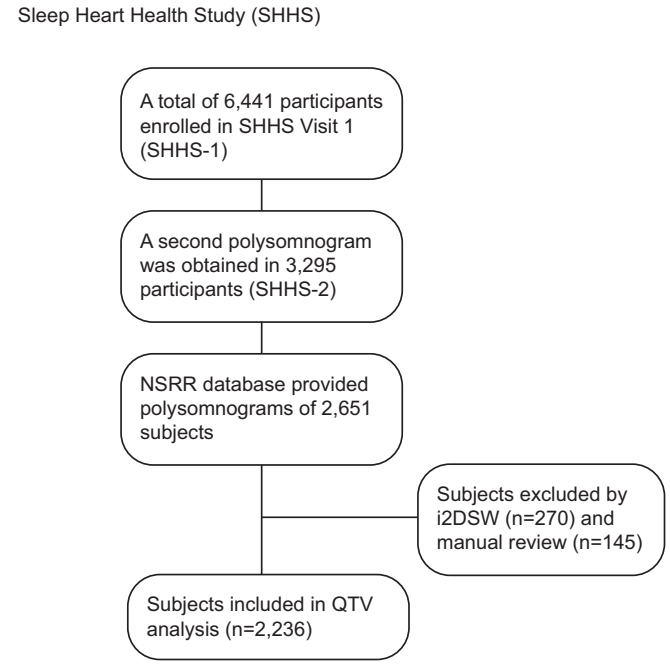

Fig. 1. Sleep heart health study (SHHS) participants enrolled; data material was provided by National Sleep Research Resource (NSRR) and processed in this study. Participants with insufficient signal quality were automatically excluded by iterative implementation of the two-dimensional signal warping (i2DSW) or by manual review from an expert. QTV, QT variability.

pants aged 40 yr and older and without history of treatment of sleep apnea were recruited between 1995 and 1998 from 9 existing prospective cohort studies. On the first visit (SHHS-1), all participants completed the baseline examination, which included an overnight polysomnogram and several interview-administered questionnaires on sleep habits and medical history. During 2001 and 2003, a second polysomnogram (SHHS-2) was obtained in 3,295 of the participants. SHHS data material was provided by the National Sleep Research Resource (NSRR) (13). The NSRR provided raw polysomnography data for SHHS-1 for 5,793 participants and for SHHS-2 for 2,651 participants (see Fig. 1).

We used the recordings from SHHS-2 because the ECG sampling rate of SHHS-1 at 125 Hz was below the requirements for QTV analysis (3). Polysomnograms were measured in an unattended setting, usually in the homes of the participants, by trained and certified technicians. Each recording contains full polysomnography, event scoring, and sleep staging according to standard methods (34). We combined sleep stages 3 and 4 to be consistent with the American Academy of Sleep Medicine standard (21). As a part of polysomnography, synchronous ECG was recorded. Polysomnograms of a small group of patients were sampled at 256 Hz instead of 250 Hz, and a notch filter of 60 Hz was applied. Polysomnographic variables included total sleep time (TST), time spent in bed (TIB), the percentage of each sleep stage, apnea-hypopnea index (AHI; number of apneas and hypopneas per hour of sleep), and mean O_2 saturation (Sa_{O_2}). AHI values were categorized as normal (AHI $<$ 5), mild sleep apnea (5 $\leq$ AHI $<$ 15), moderate sleep apnea (15 $\leq$ AHI $<$ 30), and severe sleep apnea (AHI $\geq$ 30) in further analysis. Table 1 shows clinical and sleep characteristics of the SHHS-2 cohort according to sex.

Table 1. *Clinical and sleep characteristics according to sex*

	Men	Women	*P* Value
Number of participants	1,226	1,425	
Age, yr	62.5 ± 10.1	62.3 ± 10.8	0.706
Body mass index, kg/m^2	28.6 ± 4.2	28.1 ± 5.7	
Total sleep time, min	361 ± 67	385 ± 69	<0.001
Time spend in bed, min	469 ± 71	479 ± 70	<0.001
NREM1, %	6.8 ± 4.5	4.8 ± 3.3	<0.001
NREM2, %	61.8 ± 9.8	54.3 ± 10.9	<0.001
NREM3 and NREM4, %	11.2 ± 9.1	20.0 ± 10.7	<0.001
REM, %	20.4 ± 6.6	21.1 ± 6.4	<0.01
Apnea-hypopnea index, n/h	33.2 ± 18.7	23.4 ± 16.3	<0.001
Mean O_2 saturation, %	93.8 ± 1.8	94.4 ± 2.0	<0.001

Values are means ± SE. NREM, nonrapid eye movement; REM, rapid eye movement. Comparisons between men and women were performed with an unpaired Student's *t*-test.

Table 2. *Characteristics of cardiovascular parameters according to sex*

	Men	Women	*P* Value
Number of participants	1,009	1,227	
Mean RR, ms	982.0 ± 140.4	931.5 ± 124.1	<0.001
SDRR, ms	55.0 ± 23.8	44.1 ± 17.9	<0.001
Mean QT, ms	416.1 ± 41.3	422.3 ± 37.3	<0.001
SDQT, ms	7.1 ± 6.3	8.2 ± 6.7	<0.001
$QTc_{(Bazett)}$, ms	421.5 ± 32.0	439.0 ± 30.1	<0.001
$QTc_{(Fridericia)}$, ms	419.4 ± 32.5	433.1 ± 29.9	<0.001
Mean T wave amplitude, μV	271.4 ± 166.0	188.7 ± 144.2	<0.001
QTVi, 1	−1.1 ± 0.5	−0.9 ± 0.5	<0.001
cSDQT, ms	5.5 ± 3.1	5.4 ± 3.2	0.586
cQTVi, 1	−1.3 ± 0.4	−1.2 ± 0.4	<0.001

Values are means ± SE. cQTVi, T wave amplitude-corrected QT variability index; cSDQT, T wave amplitude-corrected standard deviation of QT intervals; RR, normal-to-normal beat; QTVi, QT variability index; $QTc_{(Bazett)}$, Bazett's corrected QT interval; $QTc_{(Fridericia)}$, Fridericia's corrected QT interval; SDRR, standard deviation of RR intervals. Comparisons between men and woman were performed with an unpaired Student's *t*-test.

Table 3. *GLMM fixed factors of SHHS-2 participants showing the significant impact of sleep stage and apnea-hypopnea index on both HRV and QTV parameters and no significant impact of sex difference for SDQT and cSDQT*

	P Values				
	SDQT	SDRR	QTVi	cSDQT	cQTVi
GLMM	<0.001	<0.001	<0.001	<0.001	<0.001
Sex (men/women)	0.107	<0.001	<0.001	0.703	<0.001
Age, yr	<0.001	<0.001	0.229	<0.001	0.533
Body mass index, kg/m^2	0.105	0.883	0.438	0.935	0.697
Total sleep time, min	0.598	0.448	0.834	0.895	0.595
Time spend in bed, min	0.934	0.820	0.823	0.371	0.243
NREM1, %	0.218	0.489	0.847	0.371	0.899
NREM2, %	0.194	0.537	0.902	0.418	0.825
NREM3 and NREM4, %	0.180	0.690	0.730	0.391	0.977
REM, %	0.190	0.688	0.732	0.348	0.946
Apnea-hypopnea index (no/mild/moderate/severe)	<0.05	<0.001	<0.05	<0.01	<0.01
Mean O_2 saturation, %	0.149	<0.01	<0.001	0.252	<0.001
Mean T wave amplitude, μV	<0.001	<0.05	<0.001	<0.01	0.919
Sleep stage (wakefullness/ NREM2/NREM3/REM)	<0.001	<0.001	<0.001	<0.001	<0.001

cQTVi, corrected QT variability index; cSDQT, T wave amplitude-corrected standard deviation of QT intervals; GLMM, generalized linear mixed model; HRV, heart rate variability; QTV, QT interval variability QTVi, QT variability index; SDQT, standard deviation of QT intervals; SDRR, standard deviation of RR intervals; QTVi, QT variability index; NREM, nonrapid eye movement; REM, rapid eye movement.

Table 4. *Cardiovascular parameters during different sleep stages according to AHI [mixed ANOVA with Greenhouse-Geisser correction (factors: sleep stage, AHIc)]*

	n	Mean RR, ms	SDRR, ms	Mean QT, ms	SDQT, ms	$QTc_{(Bazett)}$, ms	$QTc_{(Fridericia)}$, ms	Mean T Wave Amplitude, μV	QTVi, 1	cSDQT, ms	cQTVi, 1
Wakefulness											
No	46	885 ± 93	45.5 ± 18.6	403 ± 32	7.8 ± 4.9	430 ± 28	421 ± 28	266 ± 200	−0.89 ± 0.53	6.0 ± 2.5	−1.06 ± 0.39
Mild	420	904 ± 120	48.4 ± 18.5	411 ± 35	8.3 ± 6.1	433 ± 28	425 ± 28	247 ± 162	−0.93 ± 0.47	6.4 ± 3.2	−1.08 ± 0.35
Moderate	643	924 ± 125	50.5 ± 21.1	410 ± 33	7.8 ± 5.5	429 ± 28	422 ± 27	252 ± 165	−0.98 ± 0.44	6.1 ± 2.6	−1.12 ± 0.33
Severe	483	931 ± 130	50.8 ± 22.0	414 ± 35	7.9 ± 5.3	430 ± 27	424 ± 27	230 ± 154	−0.96 ± 0.46	6.1 ± 2.9	−1.13 ± 0.38
NREM2											
No	46	936 ± 88	39.4 ± 15.6	418 ± 31	6.2 ± 5.0	433 ± 30	428 ± 29	238 ± 186	−0.99 ± 0.51	4.6 ± 3.1	−1.18 ± 0.38
Mild	420	952 ± 127	43.5 ± 17.7	424 ± 38	6.8 ± 6.0	436 ± 30	432 ± 30	224 ± 155	−1.02 ± 0.52	4.9 ± 3.3	−1.21 ± 0.39
Moderate	643	977 ± 132	48.7 ± 21.9	424 ± 36	6.8 ± 6.2	431 ± 31	429 ± 29	231 ± 165	−1.08 ± 0.52	4.9 ± 2.8	−1.27 ± 0.39
Severe	483	981 ± 136	53.5 ± 23.7	426 ± 36	7.3 ± 5.9	432 ± 28	429 ± 27	212 ± 155	−1.09 ± 0.51	5.3 ± 3.2	−1.29 ± 0.41
NREM3											
No	46	912 ± 90	28.8 ± 10.7	414 ± 31	5.7 ± 4.4	434 ± 30	427 ± 28	235 ± 186	−0.82 ± 0.59	4.0 ± 2.3	−1.03 ± 0.42
Mild	420	931 ± 128	32.4 ± 14.9	422 ± 38	6.3 ± 6.4	439 ± 30	433 ± 30	224 ± 155	−0.88 ± 0.59	4.5 ± 3.8	−1.08 ± 0.46
Moderate	643	954 ± 132	36.3 ± 20.2	422 ± 37	6.1 ± 6.0	434 ± 32	430 ± 31	230 ± 165	−0.94 ± 0.58	4.4 ± 2.9	−1.13 ± 0.46
Severe	483	960 ± 140	40.3 ± 21.5	424 ± 37	6.8 ± 6.4	434 ± 29	430 ± 28	212 ± 157	−0.93 ± 0.58	4.9 ± 3.5	−1.13 ± 0.48
REM											
No	46	908 ± 88	42.2 ± 16.0	414 ± 30	6.8 ± 4.4	435 ± 29	428 ± 28	234 ± 191	−0.95 ± 0.48	5.1 ± 2.7	−1.16 ± 0.35
Mild	420	927 ± 125	48.7 ± 19.9	420 ± 38	7.5 ± 6.2	438 ± 30	432 ± 30	219 ± 153	−1.04 ± 0.49	5.4 ± 3.2	−1.24 ± 0.37
Moderate	643	955 ± 130	56.0 ± 25.4	421 ± 36	7.8 ± 6.9	433 ± 31	429 ± 30	226 ± 165	−1.10 ± 0.49	5.7 ± 3.4	−1.29 ± 0.38
Severe	483	959 ± 138	61.7 ± 27.7	423 ± 36	8.6 ± 7.5	434 ± 28	430 ± 28	207 ± 154	−1.09 ± 0.50	6.2 ± 4.0	−1.31 ± 0.41
P (sleep stage, AHIc, sleep stage × AHIc)		<0.001, <0.001, >0.05	<0.001, <0.001, <0.001	<0.001, >0.05, >0.05	<0.001, >0.05, <0.001	<0.001, <0.05, >0.05	<0.001, >0.05, >0.05	<0.001, >0.05, >0.05	<0.001, >0.05, >0.05	<0.001, >0.05, <0.001	<0.001, >0.05, <0.05

AHI, apnea-hypopnea index; AHIc, categorized apnea-hypopnea index; cQTVi, T wave amplitude-corrected QT variability index; cSDQT, T wave amplitude-corrected standard deviation of QT intervals; SDQT, standard deviation of QT intervals; $QTc_{(Bazett)}$, Bazett's corrected QT interval; $QTc_{(Fridericia)}$, Fridericia's corrected QT interval; QTVi, QT variability index; SDRR, standard deviation of RR intervals; NREM, nonrapid eye movement; REM, rapid eye movement.

The prevalence of CVD was established by interview at the time of the sleep study (self-report of myocardial infarction: 7%, angina: 44%, coronary artery bypass: 5%, angioplasty: 7%, stroke: 4%, and congestive heart failure: 10%). CVD outcomes were monitored using multiple concurrent approaches, including followup interviews, written annual questionnaires or telephone contacts, surveillance of local hospital records and community obituaries, and linkage with the Social Security Administration Death Master between SHHS-1 and 2011.

RR and QTV analyses. An iterative implementation of the two-dimensional signal warping (i2DSW) algorithm (37, 38) was applied to extract RR intervals, QT intervals, and T wave amplitude from ECG. i2DSW uses a template to robustly estimate time intervals on a beat-by-beat basis. Templates for i2DSW were automatically generated and underwent a manual review by an expert to be excluded from further analysis if necessary. Automatic beat rejection (38) and RR filtering (46) were applied to exclude noisy heart beats and abnormal RR intervals (e.g., atrial fibrillation). ECG variables were processed for consecutive 5-min epochs and assigned the sleep stage that was most prevalent during that period (wakefulness, NREM2, NREM3, and REM).

Two thousand two-hundred thirty-six participants were included in further QTV analysis (excluded by automatic template generation and delineation: 194, signal quality and T wave morphology: 145, and beat rejection and RR filtering: 76; see Fig. 1). Five-min epochs with <10% exclusion of heart beats or RR intervals were used in further analysis.

For each 5-min epoch, the following variables were calculated: average normal-to-normal beat (RR) and QT intervals (mean RR and mean QT), the rate-corrected QT interval using Bazett's [$QTc_{(Bazett)}$] (6) and Fridericia's formula [$QTc_{(Fridericia)}$] (17), standard deviations of RR and QT intervals (SDRR and SDQT) (2), and the QT variability index (QTVi) (7) quantifying the relation between QTV and HRV. To consider the inverse relationship between QTV and T wave amplitude (2, 20, 36), correction formulas for SDQT and QTVi were applied (36). T wave amplitude-corrected SDQT (cSDQT) was defined as follows:

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

where $m_c = -0.36$ ms/V, the T wave amplitude normalization coefficient ($\hat{T}_{amp}$) = 300 V, and $\overline{T}_{amp}$ is the median of the absolute T wave amplitude (36). Accordingly, the QT variability index can be corrected for the T wave amplitude (cQTVi) (36) as follows:

$$\text{cQTVi} = \log_{10}\left(\frac{\frac{\text{cSDQT}^2}{\text{mean QT}^2}}{\frac{\text{SDRR}^2}{\text{mean RR}^2}}\right)$$

Besides these, the most popular parameters of QTV (2) and HRV (24, 28) were calculated to allow a systematic comparison.

Statistical analysis. Comparisons between men and woman were performed with unpaired Student's *t*-test. A generalized linear mixed model (GLMM) was used to account for the dependence structure within each patient (18). All within-individual clustered consecutive 5-min epochs are considered in GLMM. Observations within a cluster show the individual dependence between cardiovascular parameters and fixed effects (sex, age, body mass index, TST, TIB, individual sleep stage percentage, AHI, mean Sa_{O_2}, mean T wave amplitude, and sleep stage). Mixed ANOVA with the Greenhouse-Geisser correction for sphericity (19) was used to account for differences between sleep stages (within-participants effect) together with AHI (between-participants effect). To simplify the ANOVA, only GLMM fixed effects, which are significant over all analyzed parameters, were considered. The significant main effect of sleep stage was analyzed with one-way ANOVA with repeated measures (rmANOVA) and multiple comparisons. The significant main effect of categorized AHI was analyzed with one-way ANOVA with multiple comparisons. A Cox proportional hazards (CPH) model (12) was used to predict CVD death. The forward stepwise method (likelihood ratio) was used to find significant predictors (stepwise removal probability $P = 0.05$) in the CPH model. Correlation analysis between QTV and HRV parameters was performed with Pearson and Spearman correlations.

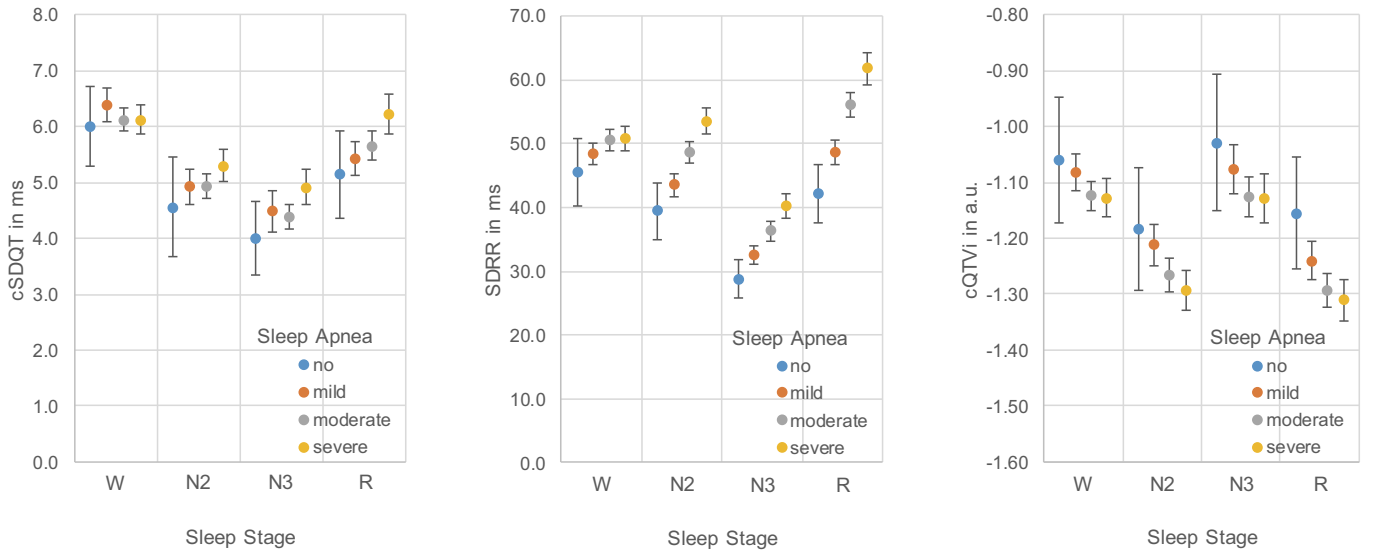

Fig. 2. Average T wave amplitude-corrected standard deviation of QT intervals (cSDQT), standard deviation of RR intervals (SDRR), and T wave amplitude-corrected QT variability index (cQTVi) characteristics according to sleep stage and categorized apnea-hypopnea index (AHI; error bars: 1.96 × SE). Numeric results and levels of significance are shown in Table 4. Comparison of T wave amplitude-corrected and non-T wave amplitude-corrected QT interval variability (QTV) parameters are shown in Fig. 3. Sleep stages were as follows: wakefulness (W), nonrapid eye movement stage 2 (N2), nonrapid eye movement stage 3 (N3), and rapid eye movement (R).

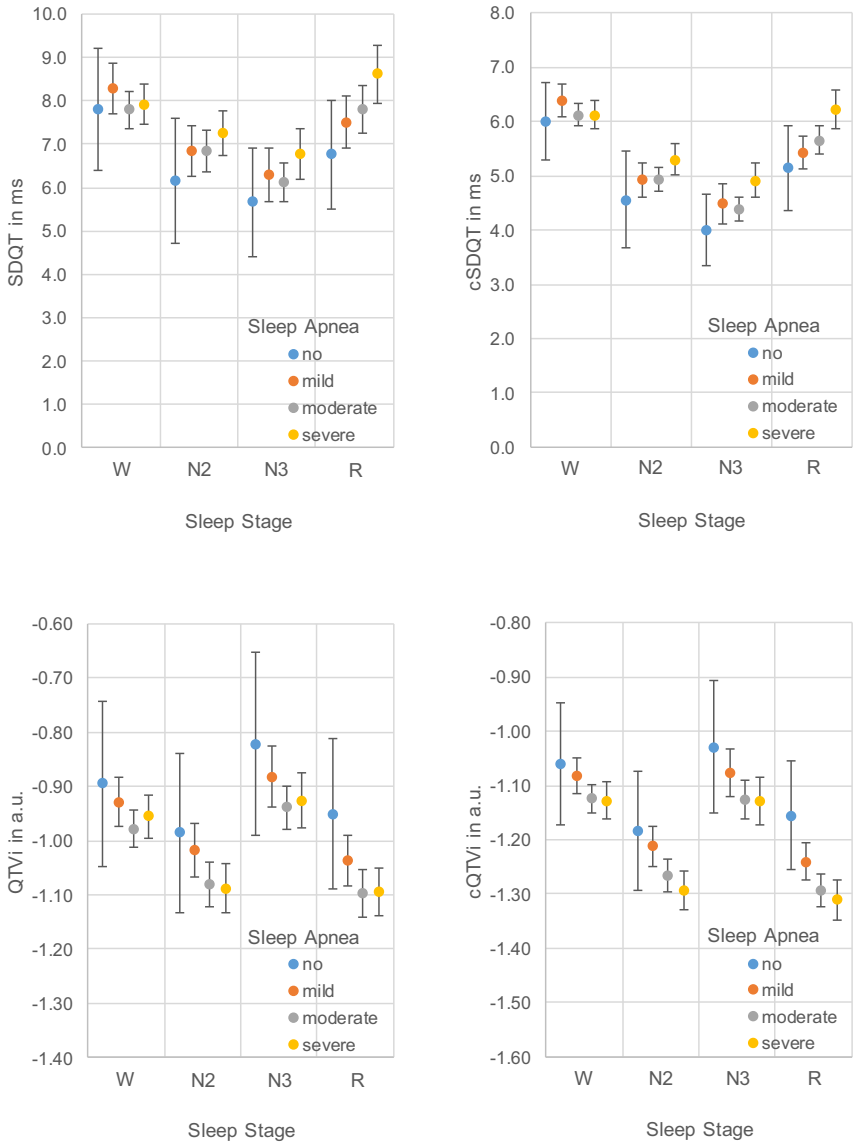

Fig. 3. Average T wave amplitude-corrected (36) and non-T wave amplitude-corrected parameter characteristics according to sleep stage and categorized apnea-hypopnea index (AHI; error bars: 1.96 × SE). Numeric results and levels of significance are shown in Table 4. Sleep stages were as follows: wakefulness (W), nonrapid eye movement stage 2 (N2), nonrapid eye movement stage 3 (N3), and rapid eye movement (R). QTVi, QT variability index; SDQT, standard deviation of QT intervals; cSDQT, T wave amplitude-corrected standard deviation of QT intervals; cQTVi, T wave amplitude-corrected QT varitability index.

RESULTS

Sex-related characteristics of demographic variables and sleep. Table 1 shows demographic variables and sleep characteristics of the study participants according to sex. Men and women did not show significant differences for age. The body mass index demonstrated as overweight (47) for both men and women. Significant differences were found for TST, TIB, the percentage of each sleep stage, AHI, and mean Sa_{O_2}. Table 2 shows characteristics of HRV and QTV parameters. SDRR was significantly ($P < 0.001$) higher in men than in women, whereas SDQT showed the opposed behavior. Mean RR was significant higher; mean QT, rate-corrected QTs, QTVi, and cQTVi were significantly lower in men compared with women. The mean T wave amplitude was ~80 μV higher in men than in women. cSDQT showed no sex-specific differences ($P = 0.586$).

Table 3 shows the results of GLMM fixed effects for SHHS-2 participants. No significant impacts of sex difference for QTV parameters were found when we corrected for T wave amplitude. Significant effects of sleep stage ($P < 0.001$) and categorized AHI ($P < 0.05$) were observed for all ECG parameters.

Effect of sleep stage and AHI on QTV and HRV measures. Mixed-effects ANOVA was used to analyze the relationship of HRV and QTV parameters with sleep stage (within-participants effect) and AHI (between-participants effect). Parameter characteristics are shown in Table 4 and Figs. 2 and 3. The effect of sleep stage was significant ($P < 0.001$) for both HRV and QTV parameters. There was a significant main effect for categorized AHI ($P < 0.01$) for SDRR. A statistically significant interaction between sleep stage and categorized AHI ($P < 0.01$) was evident in SDQT, cSDQT, and SDRR. cSDQT and SDRR decreased from wakefulness to NREM3 sleep but increased with higher sleep apnea severity in all sleep stages. In REM sleep, cSDQT and SDRR were above the level of NREM. Intersubject variability was distinctly lower in cSDQT than in noncorrected SDQT. cQTVi was lower in NREM2 and REM sleep com-

Table 5. *Cardiovascular parameters during different sleep stages (one-way ANOVA with repeated measures and multiple comparisons*

	W (n = 1,592)	N2 (n = 1,592)	N3 (n = 1,592)	R (n = 1,592)	P Value
Number of participants	1,592	1,592	1,592	1,592	
Mean RR, ms	920 ± 125 (N2, N3, R)	970 ± 132 (W, N3, R)	949 ± 133 (W, N2)	947 ± 131 (W, N2)	<0.001
SDRR, ms	49.9 ± 20.7 (N2, N3, R)	48.5 ± 21.6 (W, N3, R)	36.3 ± 19.5 (W, N2, R)	55.4 ± 25.2 (W, N2, N3)	<0.001
Mean QT, ms	411 ± 34 (N2, N3, R)	425 ± 36 (W, N3, R)	422 ± 37 (W, N2, R)	421 ± 36 (W, N2, N3)	<0.001
SDQT, ms	8.0 ± 5.6 (N2, N3)	7.0 ± 6.0 (W, N3, R)	6.4 ± 6.2 (W, N2, R)	7.9 ± 6.9 (N2, N3)	<0.001
$QTc_{(Bazett)}$, ms	430 ± 28 (N2, N3, R)	433 ± 30(W, N3, R)	435 ± 31 (W, N2)	435 ± 30 (W, N2)	<0.001
$QTc_{(Fridericia)}$, ms	424 ± 27 (N2, N3, R)	430 ± 29 (W, N3)	431 ± 30 (W, N2, R)	430 ± 29 (W, N3)	<0.001
Mean T wave amplitude, μV	244 ± 162 (N2, N3, R)	224 ± 160 (W, R)	223 ± 161 (W, R)	218 ± 160 (W, N2, N3)	<0.001
QTVi, 1	−0.96 ± 0.45 (N2, N3, R)	−1.06 ± 0.52 (W, N3)	−0.92 ± 0.58 (W, N2, R)	−1.08 ± 0.49 (W, N3)	<0.001
cSDQT, ms	6.2 ± 2.9 (N2, N3, R)	5.0 ± 3.1 (W, N3, R)	4.6 ± 3.3 (W, N2, R)	5.8 ± 3.5 (W, N2, N3)	<0.001
cQTVi, 1	−1.11 ± 0.35 (N2, R)	−1.26 ± 0.40 (W, N3, R)	−1.11 ± 0.47 (N2, R)	−1.28 ± 0.39 (W, N2, N3)	<0.001

Significant differences ($P < 0.01$) in post hoc comparison between the sleep stage under consideration and other sleep stages are indicated. Sleep stages are as follows: wakefulness (W), nonrapid eye movement stage 2 (N2), nonrapid eye movement stage 3 (N3), and rapid eye movement (R).

pared with wakefulness and NREM3 sleep. It was lower in participants with more severe sleep apnea in all sleep stages. cSDQT and SDRR increased, whereas cQTVi decreased, with sleep apnea severity category.

HRV and QTV parameters according to sleep stage are shown in Table 5. One-way rmANOVA showed significant differences ($P < 0.001$) between sleep stages for all parameters. Figure 4 shows the results for cSDQT, SDRR, and cQTVi. Comparison of T wave amplitude-corrected and non-T wave amplitude-corrected QTV parameters is shown in Fig. 5. Post hoc tests revealed significant differences ($P < 0.01$) between sleep stages. While getting into deep sleep (NREM3), cSDQT decreased significantly. In REM, cSDQT was higher than in NREM but lower than in wakefulness. cSDQT showed significant differences between all sleep stages. Intersubject variability was distinctly lower in cSDQT than in noncorrected SDQT. Cohen's d increased between all sleep stages in average 2.5 times. Uncorrected SDQT showed no effect, whereas cSDQT showed a "small to medium" effect (numeric results are shown in Table 6) (10). SDRR decreased in deep sleep (NREM3) and was higher in REM compared with wakefulness and NREM. cQTVi was significantly lower in NREM2 and REM compared with wakefulness and NREM3 (Table 7).

Table 8 shows characteristics of cardiovascular parameters according to categorized AHI. One-way ANOVA with multiple comparisons showed significant differences between categorical AHI, SDQT, cSDQT, and SDRR, which increased with sleep apnea severity. Only cSDQT and SDRR showed significant differences. In post hoc comparison, cSDQT showed significant differences ($P < 0.05$) between severe sleep apnea in categories of no, mild, and moderate sleep apnea. SDRR was significantly different ($P < 0.05$) in moderate and severe sleep apnea compared with all other sleep apnea categories. cQTVi decreased with increasing sleep apnea severity. In mild sleep apnea category, cQTVi was significantly ($P < 0.05$) higher compared with moderate and severe sleep apnea categories.

Predictive value of nocturnal QTV of CVD death. CPH models were used to test the predictive value of QTV for CVD death. Fifty of 1,576 participants died from CVD during the 5-yr followup (varying by parent cohort). The clinical variables and sleep characteristics shown in Table 1 were included in the model [to prevent the model from multicollinearity (1), heart rate or non-T wave amplitude-corrected parameters were excluded because of strong correlations)]. Hazard ratios of significant contributors to the regression model are shown in Table 9. Sex, age, TST, and cQTVi in REM sleep were independently associated with CVD death. We found only a mild correlation between predicting parameters (absolute Pearson's correlation coefficients of <0.3).

Comparison of QTV and HRV measures. The results detailed in *Effect of sleep stage and AHI on QTV and HRV measures* showed similar characteristics of QTV and HRV measures according to sleep stage. We conducted a correlation analysis (Pearson and Spearman correlation coefficients) to identify the correlation between both. Table 10 shows correlation coefficients between cSDQT and the widely used QTV (2), HRV

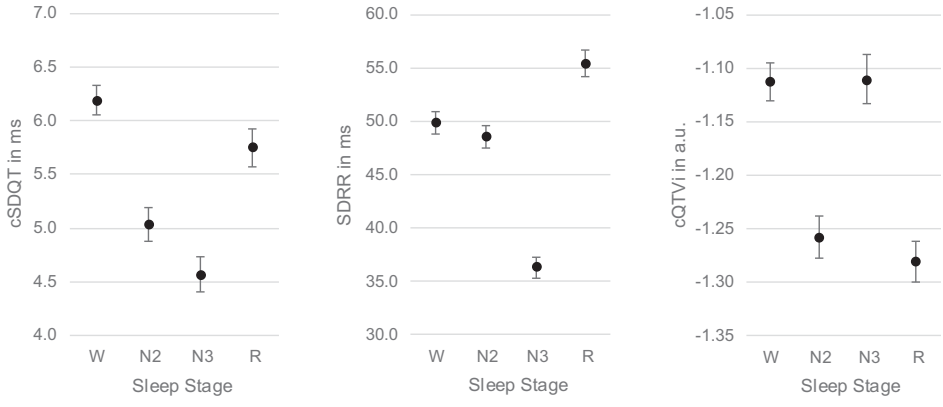

Fig. 4. Average T wave amplitude-corrected standard deviation of QT intervals (cSDQT), standard deviation of RR intervals (SDRR), and corrected QT variability index (cQTVi) characteristics according to sleep stage (error bars: 1.96 × SE). Numeric results and levels of significance are shown in Table 5. The comparison of T wave amplitude-corrected and non-T wave amplitude-corrected QT interval variability (QTV) parameters is shown in Fig. 5. Sleep stages were as follows: wakefulness (W), nonrapid eye movement stage 2 (N2), nonrapid eye movement stage 3 (N3), and rapid eye movement (R).

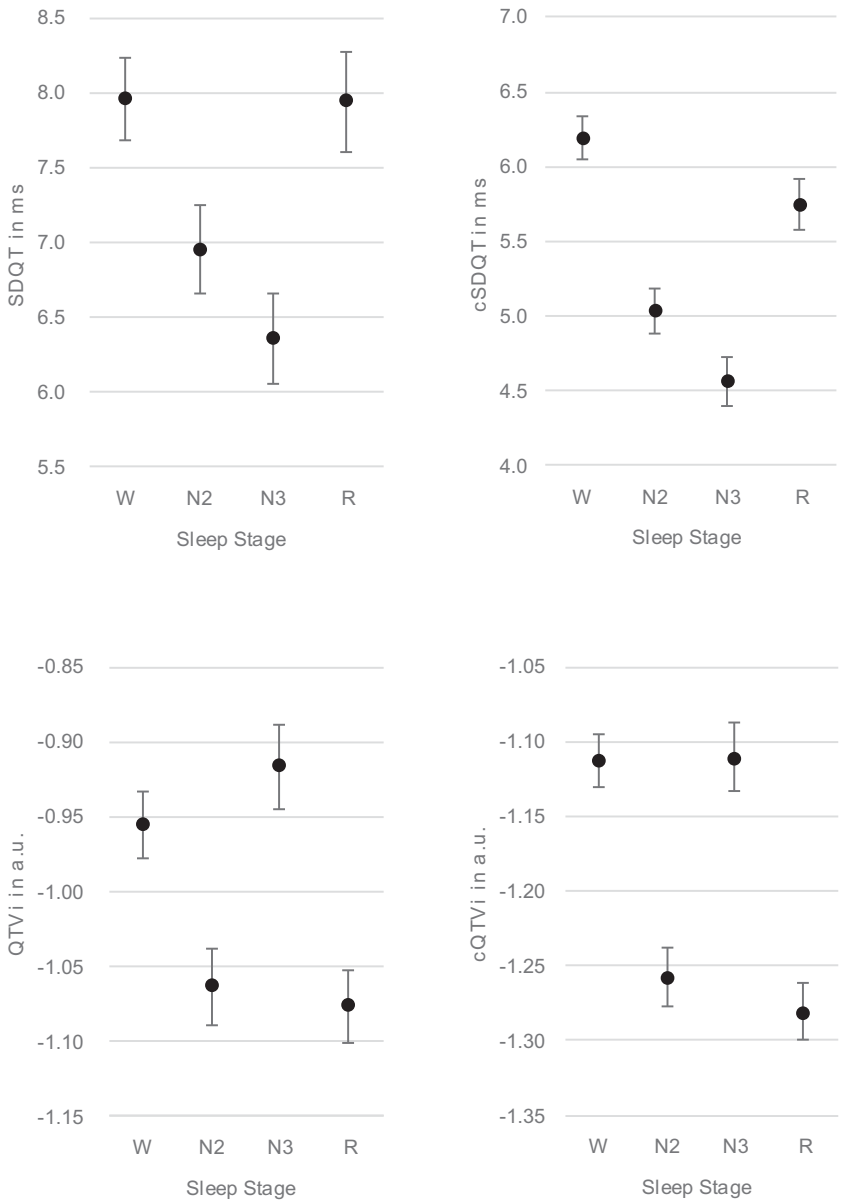

Fig. 5. Average T wave amplitude-corrected (36) and non-T wave amplitude-corrected parameter characteristics according to sleep stage (error bars: 1.96 × SE). Numeric results and levels of significance are shown in Table 5. Effect size comparisons are shown in Table 6 and Table 7. Sleep stages were as follows: wakefulness (W), nonrapid eye movement stage 2 (N2), nonrapid eye movement stage 3 (N3), and rapid eye movement (R).

Table 6. *Comparison of SDQT and cSDQT between sleep stages by effect size Cohen's d*

	W	N2	N3	R
SDQT, ms	8.0 ± 5.6	7.0 ± 6.0	6.4 ± 6.2	7.9 ± 6.9
W (8.0 ± 5.6)		0.17	0.27	0.02
N2 (7.0 ± 6.0)	0.17		0.1	0.14
N3 (6.4 ± 6.2)	0.27	0.1		0.23
R (7.9 ± 6.9)	0.02	0.14	0.23	
cSDQT, ms	6.2 ± 2.9	5.0 ± 3.1	4.6 ± 3.3	5.8 ± 3.5
W (6.2 ± 2.9)		0.40	0.52	0.12
N2 (5.0 ± 3.1)	0.40		0.12	0.24
N3 (4.6 ± 3.3)	0.52	0.12		0.35
R (5.8 ± 3.5)	0.12	0.24	0.35	

Sleep stages are as follows: wakefulness (W), nonrapid eye movement stage 2 (N2), nonrapid eye movement stage 3 (N3), and rapid eye movement (R).

(24, 28), and combined QTV-HRV (2) parameters. All absolute correlation coefficients between cSDQT and HRV were <0.5, indicating the different nature of the mentioned parameters. Moderate and strong correlations (absolute correlation coefficient > 0.5) were observed only between cSDQT and other QTV or QTV-HRV combined parameters.

DISCUSSION

Precise QT interval extraction and the opportunity of T wave amplitude correction of i2DSW enables new insights into ventricular repolarization during sleep. T wave amplitude-corrected QTV parameters showed no sex-related differences but a significant effect ($P < 0.001$) on QTV. QTV is decreased in deep sleep compared with wakefulness, is higher in REM than in NREM, and shows a distinct relation to AHI in all sleep stages. cQTVi in REM sleep was predictive of CVD death in a proportional hazards model.

Table 7. *Comparison of QTVi and cQTVi between sleep stages by effect size Cohen's d*

	W	N2	N3	R
QTVi, 1	−0.96 ± 0.45	−1.06 ± 0.52	−0.92 ± 0.58	−1.08 ± 0.49
W (−0.96 ± 0.45)		0.21	0.08	0.26
N2 (−1.06 ± 0.52)	0.21		0.25	0.04
N3 (−0.92 ± 0.58)	0.08	0.25		0.3
R (−1.08 ± 0.49)	0.26	0.04	0.3	
cQTVi, 1	−1.11 ± 0.35	−1.26 ± 0.40	−1.11 ± 0.47	−1.28 ± 0.39
W (−1.11 ± 0.35)		0.40	0	0.46
N2 (−1.26 ± 0.40)	0.40		0.34	0.05
N3 (−1.11 ± 0.47)	0	0.34		0.39
R (−1.28 ± 0.39)	0.46	0.05	0.39	

Sleep stages are as follows: wakefulness (W), nonrapid eye movement stage 2 (N2), nonrapid eye movement stage 3 (N3), and rapid eye movement (R).

Influence of sex difference in T wave amplitude on QTV. Sex differences are known to affect myocardial repolarization. Women have longer action potentials (40), reflected as longer QT intervals and augmented QTV during sleep in healthy individuals (22, 45) and those with obstructive sleep apnea (44). Our results confirm these findings. Here, we show that the T wave amplitude is flatter in women compared with men during sleep, which corroborates the findings pertaining to daytime ECG by Rautaharju and Rautaharju (33) for QTV recommended ECG leads (2). Previously reported sex differences in QTV are primarily a result of the T wave difference. By correcting for the T wave amplitude, the signal-to-noise ratio for QTV measurement becomes comparable between sexes (2).

Effect of sleep stage on QTV. Using a large cohort of study participants and a high-precision QTV measurement algorithm, we were here, for the first time, able to demonstrate sleep differences in QTV that might implicate sleep stage-specific risk for arrhythmia. Previous studies could not confirm this association (4, 22, 45), possibly because of the lack of precise QT measurement or T wave correction as well as small sample sizes. Both SDQT and SDRR decrease from wakefulness to deep sleep and increase in REM sleep. This reflects possible changes in the ANS activity, where sympathetic drive is high during wakefulness and REM sleep, whereas parasympathetic control dominates NREM sleep. Considering the ratio of QT and RR variability, cQTVi is significantly lower in wakefulness and NREM3 compared with NREM2 and REM. This finding illustrates the nonidentical characteristics of HRV and QTV across sleep stages. However, sleep characteristics of cQTVi are less interpretable than cSDQT due to the mixture of HRV and QTV. By minimizing the influence of T wave amplitude differences (see *Sex-related characteristics of demographic variables and sleep*), intersubject variability is distinctly lower in cSDQT than in noncorrected SDQT, but sleep stage characteristics are retained. Nevertheless, SDQT shows no differences between wakefulness and REM as does cSDQT, possibly due to the influence of ANS activity on T wave amplitude. Additionally, we confirm the positive correlation between the severity of obstructive sleep apnea (as determined by AHI) and QTV (4). QTV increases with the severity of AHI, intendent of sleep stage. The effect of AHI is more pronounced in HRV than in QTV measures (mixed ANOVA factor AHI is not significant for QTV measures; see Table 4), resulting in smaller QTVi and cQTVi values with increasing AHI.

Cardiovascular mortality analysis. Our observation of sleep stage-dependent QTV may be explained by the nocturnal change in sympathetic tonus. In REM sleep, both sympathetic tone and repolarization lability are augmented. Indeed, sleep stage-dependent levels of ventricular repolarization lability may trigger the onset of major cardiovascular events (25). Our CPH model points toward a predictive value of cQTVi measured during REM sleep. This observation is supported by previous studies demonstrating the direct link between excessive sympathetic activity and increased arrhythmic risk (16, 25, 39). During NREM sleep, sympathetic perturbations of ventricular repolarization are low, and the predictive value of

Table 8. *Characteristics of cardiovascular parameters according to categorized AHI (one-way ANOVA with multiple comparison)*

	Categorized AHI				
	No (0)	Mild (1)	Moderate (2)	Severe (3)	*P* Value
Number of participants	53	488	756	669	
Mean RR, ms	911 ± 105 (2, 3)	932 ± 125 (2, 3)	962 ± 134 (0, 1)	966 ± 139 (0, 1)	<0.001
SDRR, ms	38.4 ± 14.7 (2, 3)	43.7 ± 17.8 (2, 3)	49.2 ± 20.7 (0, 1, 3)	53.9 ± 23.7 (0, 1, 2)	<0.001
Mean QT, ms	412 ± 31 (3)	419 ± 37	421 ± 35	423 ± 42 (0)	0.132
SDQT, ms	6.4 ± 4.4	7.2 ± 6.1 (3)	7.3 ± 6.3	8.0 ± 6.6 (1)	0.075
$QTc_{(Bazett)}$, ms	433 ± 28	436 ± 29 (2, 3)	431 ± 30 (1)	432 ± 33 (1)	<0.05
$QTc_{(Fridericia)}$, ms	426 ± 27	430 ± 29	427 ± 29	429 ± 33	0.315
Mean T wave amplitude, μV	238 ± 188	223 ± 155	235 ± 164 (3)	217 ± 155 (2)	0.167
QTVi, 1	−0.93 ± 0.48	−0.97 ± 0.50 (2)	−1.04 ± 0.51 (1)	−1.03 ± 0.51	0.068
cSDQT, ms	4.7 ± 2.6 (3)	5.2 ± 3.1 (3)	5.4 ± 3.1 (3)	5.8 ± 3.3 (0, 1, 2)	<0.01
cQTVi, 1	−1.13 ± 0.34	−1.17 ± 0.37 (2, 3)	−1.22 ± 0.39 (1)	−1.23 ± 0.41 (1)	<0.05

Significant differences ($P < 0.01$) in post hoc comparison between the AHI category under consideration and other AHI categories are indicated.

Table 9. *Significant covariates of the Cox proportional hazards model for clinical and sleep characteristics together with cardiovascular parameters to predict cardiovascular disease death*

	Number of Participants	Hazard Ratio	95% Confidence Interval Hazard Ratio	*P* Value
Male sex	618	0.554	0.314–0.978	<0.05
Age, yr	1,576	1.166	1.119–1.215	<0.001
Total sleep time, h	1,576	0.634	0.507–0.794	<0.001
cQTVi (rapid eye movement)	1,576	2.067	1.105–3.867	<0.05

cQTVi, T wave amplitude-corrected QT variability index. The hazard ratio for continual parameters specifies the change of mortality risk per parameter unit.

cQTVi is lost. Importantly, HRV was not predictive of CVD, adding to the accumulating body of evidence for the importance of QTV for risk stratification.

Limitations. Data acquisition constitutes a potential limitation of our study. Rigorously controlled and standardized ECG acquisition procedure by the different cohorts of SHHS-2 cannot be guaranteed, which might affect T wave morphology and its analysis. Although standards have been specified in the SHHS-2 protocol, there may be a small proportion of signals that do not match these standards exactly. However, T wave amplitude-corrected QTV has been introduced by the analysis of data sets with different technical specifications (e.g., lead configuration and sampling rate) and has shown similar characteristics independent of the data specifications (36).

Another potential limitation of the proposed study is the several physiological and pathophysiological factors that could not be accounted for because they were not included in the provided data material. Notably, the influence of menopause has an impact to QTV (9) and could not be considered in *Sex-related characteristics of demographic variables and sleep*. Furthermore, the specific outcome of CVD death would bring additional impact to the predictive value of nocturnal QTV to CVD death (see *Predictive value of nocturnal QTV of CVD death*).

The statistical preconditions of stationarity in RR and QT time series were validated only by exemplary visual inspection and not rigorously tested statistically. Sleep stage transitions in particular might affect the stationarity of some of the considered epochs. This aspect should be investigated in further studies. Porta et al. (30) provide guidance on a potential procedure that could be used for this purpose.

Conclusion. We show here, for the first time, a significant impact of sleep stages on ventricular repolarization variability by means of QTV. QTV is increased in REM sleep, reflective of high sympathetic drive. Importantly, cQTVi in REM sleep may have a role in risk stratification for cardiovascular death.

Table 10. *Correlation coefficients between cSDQT and popular QTV, HRV, and QTV-HRV combined parameters during SHHS-2 recordings considering 167,498 5-min epochs (Pearson and Spearman correlation coefficients)*

	cSDQT (n = 170,932)			
Parameter	Pearson's r	P value	Spearman's ρ	P value
Nonvariability				
Mean RR	0.00	0.077	−0.03	<0.001
Mean QT	0.18	<0.001	0.13	<0.001
$QTc_{(Bazett)}$	0.23	<0.001	0.21	<0.001
$QTc_{(Fridericia)}$	0.23	<0.001	0.20	<0.001
Mean T wave amplitude	−0.08	<0.001	−0.06	<0.001
QTV				
SDQT	0.85*	<0.001	0.83*	<0.001
cSDQT	1.00*		1.00*	
QTV	0.72*	<0.001	0.82*	<0.001
nSDQT	0.72*	<0.001	0.76*	<0.001
STVQT	0.71*	<0.001	0.57*	<0.001
LTVQT	0.86*	<0.001	0.84*	<0.001
HRV				
SDRR	0.28	<0.001	0.44	<0.001
RRV	0.28	<0.001	0.48	<0.001
RMSSD	0.12	<0.001	0.22	<0.001
SDSD	0.12	<0.001	0.22	<0.001
pNN50	0.10	<0.001	0.23	<0.001
NN50 count	0.11	<0.001	0.24	<0.001
HRV triangular index	0.23	<0.001	0.36	<0.001
TINN	0.19	<0.001	0.30	<0.001
SD1	0.12	<0.001	0.22	<0.001
SD2	0.29	<0.001	0.45	<0.001
SD1/SD2 ratio	−0.10	<0.001	−0.23	<0.001
pLF	0.04	<0.001	0.09	<0.001
pHF	−0.04	<0.001	−0.09	<0.001
LF/HF ratio	0.03	<0.001	0.09	<0.001
VLF	0.12	<0.001	0.23	<0.001
LF	−0.11	<0.001	−0.17	<0.001
HF	−0.10	<0.001	−0.20	<0.001
ApEn	−0.20	<0.001	−0.32	<0.001
DFA1	0.11	<0.001	0.20	<0.001
DFA2	0.12	<0.001	0.16	<0.001
QTV-HRV				
QTVi	0.48	<0.001	0.29	<0.001
cQTVi	**0.52**	<0.001	0.34	<0.001
QTRR slope	0.24	<0.001	0.26	<0.001

ApEn, approximate entropy; cSDQT, T wave amplitude-corrected standard deviation of QT intervals; DFA1 and -2, detrended fluctuation analysis 1 and 2, respectively; HRV, heart rate variability; HF, power in high-frequency band; LF, power in low-frequency band; NN50, root mean square differences of successive RR intervals; pHF, HF power in normalized units; pLF, LF power in normalized units; QTV, QT interval variability; $QTc_{(Bazett)}$, Bazett's corrected QT interval; $QTc_{(Fridericia)}$, Fridericia's corrected QT interval; QTVi, QT variability index; RRV, squared coefficient of variation of all RR intervals; SHHS-2, Sleep Heart Health Study; RR, normal-to-normal beat; TINN, baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all RR intervals; VLF, power in very low-frequency band; SD1, Poincaré plot standard deviation perpendicular to the line of identity; SD2, Poincaré plot standard deviation along the line of identity. *Moderate and strong correlations (absolute correlation coefficient > 0.5).

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

M.S. analyzed data; M.S., M.B., H.M., and S.Z. interpreted results of experiments; M.S. and M.B. prepared figures; M.S., M.B., T.P., H.M., and S.Z. drafted manuscript.

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