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TRIGGERING OF NOCTURNAL ARRHYTHMIAS BY SLEEP DISORDERED BREATHING EVENTS

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Abstract

Objectives—This study sought to evaluate respiratory disturbances as potential triggers for arrhythmia in those with sleep-disordered breathing (SDB).

Background—SDB is associated with increased risk of atrial fibrillation (AF) and non-sustained ventricular tachycardia (NSVT) as well as a predilection for sudden cardiac death during nocturnal sleeping hours. However, prior research has not established whether respiratory disturbances operate as triggers for nocturnal arrhythmias.

Methods—Overnight polysomnograms (PSGs) from the Sleep Heart Health Study (n = 2816) were screened for paroxysmal atrial fibrillation (PAF) and NSVT. We used the case-crossover design to

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determine whether apneas and/or hypopneas are temporally associated with episodes of PAF or NSVT. For each arrhythmia, 3 periods of sinus rhythm were identified as control intervals. PSGs were examined for the presence of respiratory disturbances, oxygen desaturations, and cortical arousals within a 90-second hazard period preceding each arrhythmia or control period.

Results—Fifty-seven participants with a wide range of SDB contributed 62 arrhythmias (76% NSVT). The odds of an arrhythmia following a respiratory disturbance were nearly 18-times (OR 17.5; 95% CI 5.3–58.4) the odds of an arrhythmia occurring following normal breathing. The absolute rate of arrhythmia associated with respiratory disturbances was low (1 excess arrhythmia/40000 respiratory disturbances). Neither hypoxia nor EEG-defined arousals alone increased arrhythmia risk.

Conclusions—Although the absolute arrhythmia rate is low, the relative risk of PAF and NSVT during sleep is markedly increased shortly after a respiratory disturbance. These results support a direct temporal link between SDB events and the development of these arrhythmias.

Keywords

sleep; arrhythmia; obesity

INTRODUCTION

Sleep-disordered breathing (SDB) affects at least 5% of the adult population (1) and is associated with hypertension (2), cardiovascular disease (3), and mortality (3–4). Over the past three decades, relationships between SDB and cardiac arrhythmias have been explored (5–10). SDB increases the risk of incident atrial fibrillation (11) and the risk of ventricular arrhythmias (12–13), which may relate to the increased risk of sudden cardiac death (SCD) during overnight sleeping hours of those with SDB (14). Proposed mechanisms to explain these relationships include the potentially pro-arrhythmic contributions of apnea-induced hypoxia and increased sympathetic nervous system activity, both acutely and in a tonic fashion (12, 15–17). However, a causal link between SDB and arrhythmia has not yet been established. Confirming a temporal relationship between SDB events and specific arrhythmia episodes could support causality and would have important implications for establishing therapeutic endpoints and refining cardiovascular risk stratification, as well as for elucidating the pathophysiology of arrhythmogenesis in SDB.

Recent data from the Sleep Heart Health Study (SHHS) demonstrated a higher prevalence of atrial fibrillation (AF) and non-sustained ventricular tachycardia (NSVT) in those with severe SDB (Apnea-Hypopnea Index [AHI] $\geq$ 30 events/hour) relative to those with low levels of SDB (AHI < 5 events/hour); these effects persisted after adjusting for self-reported coronary heart disease (CHD) and CHD risk factors (10). However, this comparison of extremes of SDB did not address whether intermediate levels of SDB were also associated with arrhythmias, and inferences were limited by the cross-sectional design. Using the case-crossover design, an analytic approach developed to study the effects of transient exposures on the risk of acute events (18–19), we now aim to extend prior research by investigating, across the full range of SDB, whether respiratory disturbances can trigger AF or NSVT.

METHODS

Study population

All data were ascertained from the SHHS, a multicenter longitudinal study designed to investigate the cardiovascular consequences of SDB (20–21). Of the 3295 polysomnograms (PSGs) performed as part of the second SHHS examination, 2816 records underwent detailed review of the EKG channel with the aim of identifying studies with at least one episode of paroxysmal AF (PAF) or NSVT occurring during the sleep period. This sample consisted of

all records with an AHI < 30 events/hour that were technically satisfactory (n = 2569) and a sample of technically satisfactory studies (n = 247) with an AHI ≥ 30 events/hour from subjects with BMI between 18–40 kg/m^2 not on CPAP therapy that had been included in a prior study comparing arrhythmias across extreme levels of SDB (10). This approach identified 57 participants with PAF or NSVT.

Cohort and PSG measurements

Standardized questionnaires from the second SHHS examination conducted between 2001–2002 were used to collect demographic/anthropomorphic data (age, gender, race/ethnicity, height, weight), self-reported cardiovascular risk-factors/disease (hypertension, diabetes mellitus, smoking status, heart failure, history of CHD [defined as prior myocardial infarction or percutaneous/surgical revascularization], and arrhythmia-related data [use of anti-arrhythmic drugs, prior pacemaker implantation]). PSGs were performed and scored as described previously (10,21). PSG summary data included total sleep time, AHI (the average number of apneas plus hypopneas per hour of sleep), sleep stage distributions, arousal index, average oxygen saturation during sleep, and percentage of sleep time spent below 90% oxygen saturation.

Study design

To investigate whether respiratory disturbances can trigger arrhythmic events, the case-crossover study design was applied (18–19). This method analyzes the risk of an event occurring in the context of a transient exposure, with subjects serving as their own controls. For each case that is identified, a hazard period, during which subjects are presumed to be at increased risk for events, is examined for the presence of the exposure of interest. Correspondingly, referent (control) periods are also examined for the exposure of interest. Subjects serve as their own controls during periods when they are not having an event, and thus the association between the exposure and the event is not confounded by subject characteristics that remain essentially constant during the observation period (age, gender, BMI, size of cardiac chambers, for example). In the current study, the 'events' are arrhythmias (PAF and NSVT), the 'exposures' are respiratory disturbances (apneas or hypopneas), and the ‘referent’ periods are derived from time spent in sinus rhythm (Figure 1).

We defined the hazard period as 90 seconds, which incorporates estimates of average respiratory disturbance duration (25–30 seconds), lag time between event cessation and nadir oxygen saturation (~ 15–30 seconds), the delay between nadir oxygen saturation and resolution of hypoxia (~ 10–15 seconds), and a short time after resolution of hypoxia during which its physiologic effects are still measurable (~ 10 seconds). This sequence of events, as well as the duration of its components, is derived from SHHS data and from prior physiologic and clinical studies (15–17,22–26).

To identify referent periods for each arrhythmia, we selected randomly 3 epochs of sinus rhythm from the same subject that met the following criteria: (1) equal in duration to the hazard period (90 seconds), (2) same sleep stage (1, 2, 3–4, REM) as the corresponding arrhythmic event, (3) < 25% ectopic beats, (4) absence of complex ventricular ectopy (bigeminy, trigeminy, quadrageminy, couplets – as defined in 10) and pauses > 2 seconds. The strategy of matching on sleep stage was used to avoid confounding from state-dependent influences such as REM-related sympathetic nervous system surges. To minimize the effects of autocorrelation of exposure and the ‘carryover effect’ (27), the referent periods were further restricted to those occurring at least 6 minutes (the duration of 4 hazard periods) prior to the onset of the arrhythmic event. Since it is unknown whether arrhythmias can affect the occurrence of respiratory disturbances, we used a unidirectional design; the hazard period and all referent periods were selected such that they occur prior to the arrhythmia of interest.

Arrhythmia identification

EKG data were obtained from a single bipolar lead (lead I) sampled at 250 Hz collected as part of the overnight PSG. This channel was reviewed manually for arrhythmias using the CompuMedics EDF Studio® viewer. The channels that provide information on respiratory disturbances were disabled so that arrhythmias were identified without knowledge of surrounding respiratory status; these channels were also disabled during the referent period selection process. Episodes of NSVT, defined as ≥ 3 consecutive ventricular ectopic beats with an average heart rate of ≥ 100 beats/minute, and PAF, defined as a period of irregular, narrow complex rhythm without evidence of organized atrial activity, were identified. Other recorded parameters included: the absolute time of arrhythmia onset, duration of arrhythmia (the interval between its onset and the first QRS complex that appeared to be a normally conducted impulse originating at the sinus node), and the concurrent sleep stage. Most participants had a single arrhythmic event. However, 7 subjects had multiple arrhythmias over the course of their study. In these cases, one arrhythmia from each sleep state (NREM or REM) was chosen at random and treated as an independent event in the analysis. Of these 7 subjects, two had all of their arrhythmias in NREM and thus contributed one event each and five subjects had at least one arrhythmia in NREM and REM and therefore each contributed two events to the final dataset.

Exposure assessment

The primary exposure was a respiratory disturbance (apnea or hypopnea) defined solely by changes in amplitude of the airflow and effort signals for ≥ 10 seconds, as described previously (20–21). For each arrhythmia, the associated hazard and referent periods were examined for respiratory disturbances. For each of those respiratory disturbances, the following characteristics were recorded: duration of the apnea or hypopnea, attendant nadir oxygen saturation (occurring within 25 seconds of the disturbance's termination), whether an EEG-defined arousal occurred within 3 seconds of the disturbance's termination, and the interval between the onset of an associated arrhythmia (if present) and the termination of the respiratory disturbance. If any part of a respiratory disturbance occurred during a hazard or referent period, the individual was considered 'exposed' during that period. For hazard and referent periods during which no respiratory disturbance occurred, the nadir oxygen saturation and the presence or absence of an EEG-defined arousal over the 90-second window were also recorded.

Secondary exposures included EEG-defined arousals and several definitions of hypoxia based on nadir oxygen saturation. We also created a 4-level variable to evaluate exposure to different levels of respiratory disturbance severity: (1) no respiratory disturbance (reference), (2) respiratory disturbances with neither an arousal nor hypoxia (defined as nadir $SpO_2 \leq 92\%$), (3) respiratory disturbances linked to a nadir $SpO_2 \leq 92\%$, and (4) respiratory disturbance linked to an EEG-defined arousal.

For quality control purposes, a randomly chosen subset (n = 10) of PSGs was examined independently by two investigators (KM and RM). For this subset, no inter-observer differences were noted in arrhythmia detection or exposure classification of hazard/referent periods.

Absolute arrhythmia rate assessement

To provide context for the relative risk estimates derived from the case-crossover results, a crude absolute rate of arrhythmia associated with respiratory disturbances was estimated using data from the SHHS cohort. The rate of arrhythmia during the hazard period (R_h) was defined as the number of arrhythmias occurring during the hazard period (A_h) divided by the total exposure time (T_e): $R_h = \frac{A_h}{T_e}$. The total exposure time (T_e) was calculated as the product of the total number of respiratory disturbances experienced by the entire cohort and the exposure time

per respiratory disturbance (h): $T_e = \left[\sum_{i=1}^{N} AHI_i \times TST_i\right] \times h$, where h is defined as the 90-second hazard period, N is the total number of participants in the cohort, and AHI_i and TST_i are the apnea-hypopnea index and the total sleep time, respectively, of a given participant. The rate of arrhythmia outside the hazard period (R_o) was defined as the number of arrhythmias occurring during non-exposed periods (A_o) divided by the total unexposed time (T_u): $R_o = \frac{A_o}{T_u}$. The total unexposed time (T_u) was computed by subtracting the total exposed time (T_e) from the aggregate TST of the entire cohort: $T_u = \left(\sum_{i=1}^{N} TST_i\right) - T_e$. The absolute rate difference was taken as the difference between the rate of arrhythmia within the exposure period and the rate of arrhythmia outside of the exposure period ($R_h - R_o$). In order to make this absolute rate difference estimate more readily interpretable, we used the exposure period duration to convert the rate difference (excess arrhythmias per unit of sleep duration) to the number of respiratory disturbances associated with one excess arrhythmia (analogous to the 'number needed to treat – NNT'). It should be noted that, unlike the matched odds ratio from the case-crossover design, this estimate has no inherent matching and therefore does not control for any confounding variables (demographics, medical history, sleep characteristics).

Statistical analysis

Univariate descriptive statistics were used to summarize subject characteristics. Bivariate comparisons of characteristics for participants with and without arrhythmia were evaluated using the Pearson Chi-square test for categorical data, the two-sample t-test for normally distributed measures, and the Wilcoxon rank sum test for skewed measures. All subsequent analyses were restricted to the participants with arrhythmia. Descriptive analyses were stratified by type of arrhythmia (PAF or NSVT) and by period type (hazard or referent). To estimate the odds of an arrhythmia occurring during the hazard period following a respiratory disturbance relative to the odds of an arrhythmia occurring during normal nocturnal breathing, the Mantel-Haenszel matched odds ratio and conditional logistic regression, stratified on the arrhythmia event, were used. For the 5 subjects that contributed 2 arrhythmias, each arrhythmia was treated as coming from an independent individual. The main analyses were repeated stratified on the individual and yielded similar results. Exploratory analyses were stratified by the type of arrhythmia (PAF or NSVT) and by sleep state (NREM vs REM). We also examined the two-way interaction between sleep state and the exposure to determine whether the odds ratio for an arrhythmia varied by NREM/REM sleep state. Results are summarized using odds ratios and 95% confidence intervals; two-sided p-values are reported. Analyses were conducted using SAS version 9.1.

RESULTS

Cohort and sleep study characteristics

Demographic characteristics, relevant aspects of medical history, and selected PSG features of the cohort, stratified by arrhythmia status, are shown in Table 1. The sample that demonstrated arrhythmias of interest (n = 57) was elderly (72.1 ± 10.1 years old), predominantly Caucasian (77%), and just over half was male (56%). Risk factors for heart disease were prevalent; nearly half (49%) had hypertension, 39% were obese, and 44% were active or former smokers. Eighteen percent of those with arrhythmia reported a history of CHD and 2 individuals reported a history of heart failure. Medication data were available for 52 participants; of these, 2 reported taking anti-arrhythmic drugs (one each for Class IB and Class III), and 8 reported using beta-blockers. The TST by PSG was approximately 6 hours, with

just under 20% of that time spent in REM sleep (19.0 ± 6.3%). The median AHI was 13.6 events/hour (IQR 6.2–25.5 events/hour). Participants with arrhythmia were older, had a higher proportion of sleep time with $SpO_2 < 90\%$, and had slightly higher AHI than those without arrhythmia. In addition, the arrhythmia group had an increased prevalence of hypertension, coronary heart disease, and high AHI (AHI ≥ 30 events/hour) compared to the group without arrhythmia.

Arrhythmia characteristics

Features of the 62 detected arrhythmias are shown in Table 2. The majority of reported arrhythmias were NSVT (76%) and approximately two-thirds of arrhythmias occurred in NREM sleep (68%). Median arrhythmia duration was 7 seconds for PAF and 3 seconds for NSVT. The longest episode of PAF lasted nearly 5 minutes. The next longest episode was considerably shorter at 12 seconds. The longest episode of VT lasted 35 seconds with the next longest episode lasting 19 seconds.

Respiratory disturbance characteristics

A respiratory disturbance occurred in 44 of the 62 hazard periods (71%) and in 65 of the 186 referent periods (35%). The overall characteristics of respiratory events in the hazard and referent periods were similar; in both periods, the majority of respiratory events were hypopneas (77%). Only one central apnea was identified and it occurred in a referent period. Of the 44 respiratory events occurring in hazard periods, 18 (41%) occurred in REM sleep. Of the 65 respiratory events occurring in referent periods, 39 (60%) occurred in REM sleep. Respiratory disturbance duration, associated nadir oxygen saturation, and the proportion with EEG-defined arousals were similar for respiratory disturbances occurring in hazard and referent periods (data not shown).

Case-crossover analysis

Table 3 shows the distribution of matched sets (one hazard period and three control periods) according to the presence of a respiratory disturbance. Of the 62 sets, 27 sets were concordant on the exposure. Of those 27 concordant sets, 15 sets did not have a respiratory disturbance during the hazard period and likewise did not have a respiratory disturbance during any of the referent periods; 12 sets had a respiratory disturbance during the hazard period and also had respiratory disturbances during all 3 referent periods. The remaining 35 sets showed various levels of discordance on the exposure; for example, 5 sets had a respiratory disturbance during the hazard period, but only during 2 of the 3 referent periods. The odds of a nocturnal arrhythmia occurring within the 90-second hazard period following a respiratory disturbance was over 17-fold greater than the odds of an arrhythmia occurring during normal nocturnal breathing (Mantel-Haenszel matched odds ratio 17.8; 95% CI 5.0–63.0).

The conditional logistic regression results are shown in Table 4 for the primary analysis and several exploratory analyses. The odds ratio (OR) computed using conditional logistic regression was similar to the Mantel-Haenszel odds ratio (OR 17.5; 95% CI 5.3–58.4). The results of the secondary analyses stratified on the individual, rather than the arrhythmia event, were consistent with the primary finding. Analyses stratified by type of arrhythmia showed that the magnitude of the association for PAF and NSVT was similar to that for the overall group. An association remained for arrhythmias occurring during NREM sleep (OR 14.2; 95% CI 4.2–48.0), but could not be estimated for REM events due to the small number of discordant sets. However, there was no statistical evidence of an interaction between sleep stage and respiratory disturbance ($p = 0.99$).

Exploratory analyses examined the association between arrhythmias and secondary exposures. Significant associations between arrhythmias and respiratory disturbances were seen

regardless of whether respiratory disturbances were associated with nadir $SpO_2 \leq 92\%$ or arousal (Table 4). In contrast, when the exposure was defined as hypoxia or EEG-defined arousal regardless of the presence of a respiratory disturbance, the associations were weak, inconsistent, and not statistically significant (data not shown).

Absolute arrhythmia rate estimation

For the entire cohort of 2816 participants, the rate of arrhythmia during exposed periods was 3.9 per 1000 hours of sleep. The rate of arrhythmia during unexposed periods was 2.9 per 1000 hours of sleep. Therefore, the absolute rate of arrhythmia associated with respiratory disturbances was estimated to be 1 excess arrhythmia per 1000 hours of sleep (with a median AHI of 23 events/hour) or 1 excess arrhythmia per 40000 respiratory disturbances. Thus, an individual with moderate SDB (AHI of 30 events/hour) who sleeps an average of 8 hours per night would be estimated to have 1 excess arrhythmia every 5.6 months or 2 per year.

DISCUSSION

The main finding of the present study is the nearly 18-fold increase in the relative risk of nocturnal arrhythmia within 90 seconds (a physiologically-defined interval) following a respiratory disturbance in individuals with a broad range of SDB severity. Prior clinical and epidemiologic studies have established an association between SDB and arrhythmia (5–7,10, 12–13), but the temporal relationship between the two, particularly involving PAF and NSVT, has not previously been characterized. A small study in patients with central sleep apnea and heart failure demonstrated suppression of PVCs in the subset that responded to CPAP therapy (28), suggesting indirectly a link between central apneas and ventricular ectopy. A small study of patients with severely depressed LV systolic function, severe SDB, and previously demonstrated ventricular ectopy on Holter monitoring demonstrated that PVCs occurred more frequently in the apneic phase of obstructive apneas than during other phases of the respiratory cycle (29). Another study showed a higher frequency of apnea-associated compared to nonapnea-associated arrhythmias in 8 patients with SDB, left-ventricular dysfunction, and prior ICD placement (13). However, none of these studies quantified the extent to which sleep-related respiratory disturbances operated as triggers for arrhythmias and none investigated PAF as an arrhythmia of interest.

A prior study from the SHHS reported an increased odds of arrhythmias among subjects with severe SDB (AHI $\geq$ 30 events/hour) compared to those with an AHI < 5 events/hour (10). However, that analysis did not address the propensity for arrhythmias in individuals with more moderate levels of SDB, as is found more frequently in the general population. The current report analyzed all records of participants with an AHI < 30 events/hour. The majority of identified arrhythmias occurred among those with only moderate levels of SDB (AHI 5–30 events/hour). As shown by the moderate median AHI of our cohort and the finding that most of the respiratory disturbances preceding arrhythmias were hypopneas (as opposed to apneas), neither the severity of SDB nor the severity of individual respiratory disturbances needs to be extreme in order to increase the risk of arrhythmia.

In this study, we attempted to identify the relative contributions of hypoxia and arousal to arrhythmogenesis. We identified all ‘respiratory disturbances’ based solely on changes in airflow and effort signal amplitude, without requiring a linked desaturation or arousal. We then secondarily assessed whether the extent of linked desaturation or arousal was related to propensity for PAF or NSVT. In these analyses, the ORs for arrhythmia did not vary according to whether nadir saturation levels fell below 92% nor did they vary according to whether respiratory disturbances were associated with a cortical arousal. However, since more than one-half of the respiratory disturbances in the hazard/referent periods were associated with a desaturation of $\geq$ 3% (a commonly used clinical criterion) and the mean desaturation for all

respiratory disturbances that occurred in hazard/referent periods was ~ 4%, it is possible that some degree of hypoxic stress was contributory to the observed associations. The overall small number of respiratory disturbances may have limited the ability to discern effects associated with arousal or desaturation. Nonetheless, our data also raise the possibility that additional mechanisms, such as large changes in intrathoracic pressure and stimulation of baroreflexes, may contribute to the link between respiratory disturbances and arrhythmias (25).

In interpreting our findings, it is important to distinguish between relative and absolute risk. The overall frequency of arrhythmias in this community-based cohort was very low while the frequency of respiratory disturbances was moderate. Crude estimates of absolute arrhythmia rate suggest that 1 excess arrhythmia may occur per 1000 hours of sleep in subjects with a median AHI of 23 events/hour. The high and growing prevalence of SDB, which influences the effective 'hazard period' in the population, suggests that respiratory disturbances may contribute to a considerable number of excess episodes of PAF or NSVT. In addition, it is possible that risk is not evenly distributed in the population and that the rate of SDB-associated arrhythmias may be even higher among individuals with impaired cardiac function or with other risk factors that enhance their vulnerability to physiological stressors.

The high relative risk may provide insights into prior studies demonstrating adverse cardiovascular outcomes in patients with SDB, including AF. Our results reveal a significant association between the risk of PAF and the presence of a respiratory disturbance within the pre-defined hazard period. Significant associations between AF and SDB have been previously reported (9,30); specifically, SDB is a risk factor for incident AF (11) and for recurrence of AF following electrical cardioversion (31). Repeated exposures to intervals of relatively high risk for PAF, both within a given night and over many nights, may result in an increasing cumulative burden of discrete PAF episodes over time. Each of these paroxysms may increase the propensity for further and sustained episodes of AF due to electrical remodeling within the atria (32). Therefore, untreated SDB may serve as an ongoing source of AF stimulation leading ultimately to initiation or recurrence of clinically significant arrhythmia. Correspondingly, it is plausible that treatment of underlying SDB may inhibit progression of sub-clinical PAF to a more detrimental form of the arrhythmia. A marked rise in the prevalence of AF is anticipated in coming years with ~ 60% of that increase estimated to be attributable to obesity (33). Our data, which temporally link SDB events and the risk of PAF, suggest that unrecognized SDB may be a contributing factor to the projected increase in AF due to obesity.

Our finding of increased risk of NSVT during the hazard period following a respiratory disturbance may provide further insight into the observed nocturnal predominance of sudden cardiac death in SDB patients (14). For those with structural heart disease, the risk of SCD is higher in those with NSVT relative to those without it (34–35). Therefore, our findings raise the possibility that, in a sufficiently susceptible population, SDB increases the nocturnal risk of SCD by providing frequent nocturnal exposure to a stimulus that increases the likelihood of ventricular arrhythmia. This possibility is supported by a recent study of heart failure patients with ICDs that demonstrated that appropriate anti-tachycardia therapies for VT or VF were delivered more frequently in those with SDB than in those without SDB; this relationship was present only during sleeping hours (36). Furthermore, even in the absence of structural heart disease, SDB has been found to be highly prevalent in those with frequent PVCs and/or VT (37); our results are consistent with this observation as well.

A strength of the present study was the utilization of the case-crossover design. Since individuals served as their own controls, this approach essentially eliminated confounding by subject characteristics that remained constant during the observation period, a challenge in all prior work in this area. In addition, the study participants are part of a community-based cohort,

rather than 'patients' with a homogenous cardiovascular profile, and represent the full spectrum of SDB severity; both of these features enhance the generalizability of our findings.

A limitation of the current study is the small number of detected arrhythmias (38), which reduced the ability to detect potential effect modification by underlying risk factors, subject characteristics, and sleep state effects. However, the case-crossover design allows for analytic efficiency as well as a minimum of confounding for between-individual comparisons. Detailed information regarding daytime arrhythmia prevalence and temporal distribution are not readily available, rendering impractical a direct comparison between the arrhythmia profiles of our cohort during wakefulness and sleep. We limited our assessment of nocturnal arrhythmias to PAF and NSVT; inclusion of complex ventricular ectopy as part of the analysis would have increased our sample size, perhaps at the expense of direct clinical impact of the results.

In summary, this study demonstrates that, across the range of SDB, the risk of clinically important nocturnal arrhythmias is markedly increased shortly after the occurrence of apneas and hypopneas during sleep. This work provides further evidence that intermittent airflow obstruction may lead to clinically important adverse cardiac effects, and that such effects may occur even in individuals without severe levels of SDB. Further research is needed to evaluate the ability of pharmacotherapy and/or SDB treatment to modify these associations.

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ABBREVIATIONS

AHI	apnea-hypopnea index
CHD	coronary heart disease
NREM	non-rapid eye movement
NSVT	non-sustained ventricular tachycardia
PAF	paroxysmal atrial fibrillation
PSG	polysomnogram
REM	rapid eye movement
SCD	sudden cardiac death
SDB	sleep-disordered breathing
SHHS	Sleep Heart Health Study

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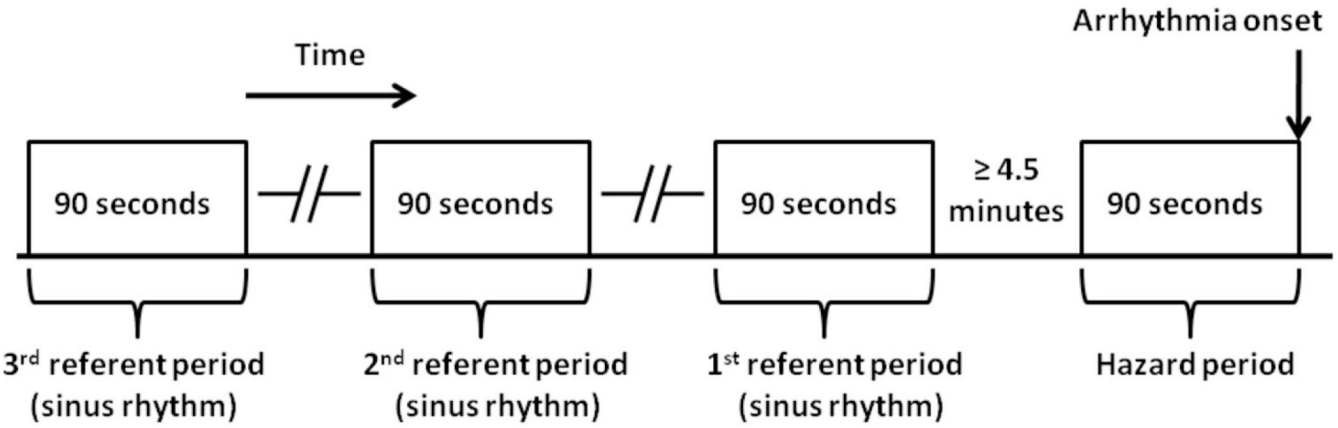

Figure 1. Design of case-crossover analysis

The 90-second hazard period immediately preceding an arrhythmia is evaluated for respiratory disturbances. Three randomly chosen referent periods of sinus rhythm, which precede the index arrhythmia by at least 6 minutes, are also examined for respiratory disturbances. If any part of a respiratory disturbance occurs in a hazard or referent period, that period is considered 'exposed'.

Table 1

Sample characteristics*

Characteristic	Entire Sample (n = 2816)	No Arrhythmia (n = 2759)	PAF or NSVT (n = 57)
Demographics			
Age (years)†	68.0 ± 10.0	67.9 ± 10.0	72.1 ± 10.1
Female	1559 (55%)	1534 (56%)	25 (44%)
Caucasian	2126 (76%)	2082 (76%)	44 (77%)
African-American	184 (6%)	179 (6%)	5 (9%)
Other ethnicity	506 (18%)	498 (18%)	8 (14%)
BMI			
Overall (kg/m^2)	29.2 ± 5.2	29.2 ± 5.2	29.1 ± 4.9
Obese (BMI ≥ 30 kg/m^2)	1059 (38%)	1037 (38%)	22 (39%)
Self-reported cardiovascular risk factors/disease			
Hypertension‡	936 (33%)	908 (33%)	28 (49%)
Diabetes	275 (10%)	268 (10%)	7 (12%)
Current or former smoker	1399 (50%)	1374 (50%)	25 (44%)
Coronary heart disease‡	227 (8%)	217 (8%)	10 (18%)
Heart failure	40 (1%)	38 (1%)	2 (4%)
Arrhythmia therapy§			
Beta-blocker	294 (10%)	286 (10%)	8 (15%)
Anti-arrhythmic drug	46 (2%)	44 (2%)	2 (4%)
Permanent pacemaker	18 (1%)	17 (1%)	1 (2%)
Polysomnography data			
Total sleep time - TST (minutes)	373 ± 70	373 ± 70	364 ± 76
REM (%)	20.5 ± 6.8	20.5 ± 6.8	19.0 ± 6.3
Average SpO_2 during sleep (%)	94.1 ± 1.8	94.1 ± 1.8	93.9 ± 2.1
SpO_2 < 90% (% TST)‡	0.6 (0.1–2.9)	0.6 (0.1–2.9)	1.1 (0.2–6.2)
Overall AHI (events/hour)‡	10.8 (5.6–19.0)	10.7 (5.6–18.9)	13.6 (6.2–25.5)
Low: AHI < 5	605 (21%)	595 (21%)	10 (18%)
Intermediate: AHI 5–29	1964 (70%)	1928 (70%)	36 (63%)
High: AHI ≥ 30‡	247 (9%)	236 (9%)	11 (19%)
Arousal index (events/hour)	15.7 (11.2 – 21.7)	15.7 (11.3 – 21.5)	18.3 (11.0 – 24.0)

Counts and percentages are shown for categorical variables.

Mean ± standard deviation are shown for normally distributed measures

Median (25th–75th percentile) are shown for non-normally distributed variables

AHI apnea-hypopnea index

BMI body-mass index

PAF paroxysmal atrial fibrillation

NSVT non-sustained ventricular tachycardia

REM rapid eye movement sleep

SpO_2 oxygen saturation

* all covariate data were obtained from the second Sleep Heart Health Study exam other than for 5 participants from one site for which only data from the baseline exam were available

† $p < 0.01$ for comparison between arrhythmia and non-arrhythmia groups

‡ $p < 0.05$ for comparison between arrhythmia and non-arrhythmia groups

§ $n = 52$ (data not available for 5 participants from one site)

Table 2

Arrhythmia characteristics

		Total	PAF	NSVT
Events		62	15	47
Duration distribution (seconds)		4 (2–7)	7 (3–9)	3 (2–5)
Sleep stage				
	NREM	42 (68%)	12 (80%)	30 (64%)
	REM	20 (32%)	3 (20%)	17 (36%)

Counts and percentages are shown for categorical variables.

Data are median (25th–75th percentile) for non-normally distributed variables

NREM non-rapid eye movement sleep

NSVT non-sustained ventricular tachycardia

PAF paroxysmal atrial fibrillation

REM rapid eye movement sleep

Table 3

Exposure to a respiratory disturbance during the hazard period and 3 matched referent periods (n = 62 matched sets)*

Number of referent periods with a respiratory disturbance	Respiratory disturbance during the hazard period?	
	Yes	No
0 periods with a respiratory disturbance	**12**	*15*
1 period with a respiratory disturbance	**15**	**2**
2 periods with a respiratory disturbance	**5**	**1**
3 periods with a respiratory disturbance	*12*	**0**

* **Bold and underlined** entries indicate discordant sets; *italics* indicate concordant sets

Table 4

Risk of arrhythmia following a respiratory disturbance compared to the risk of arrhythmia during normal nocturnal breathing

	Number of arrhythmias included in each analysis	Odds Ratio (95% CI)
Primary Overall Analysis	**62**	**17.5 (5.3–58.4)**
Sub-Analyses		
By Arrhythmia type		
PAF	15	17.9 (2.2–144.2)
NSVT	47	17.4 (4.0–75.7)
By Sleep stage		
NREM	42	14.2 (4.2–48.0)
REM	20	*
By Respiratory disturbance subtype		
No respiratory disturbance	18	-reference-
Respiratory disturbance without hypoxia (nadir $SpO_2 \leq 92\%$) or arousal	14	24.1 (5.4–106.6)
Respiratory disturbance with hypoxia	20	13.6 (3.7–50.6)
Respiratory disturbance with arousal	10	21.8 (4.5–106.3)

CI confidence interval

EEG electroencephalogram

PAF paroxysmal atrial fibrillation

NREM non-rapid eye movement sleep

NSVT nonsustained ventricular tachycardia

REM rapid eye movement sleep

SpO_2 oxygen saturation

* unable to be calculated