Association of Nocturnal Arrhythmias with Sleep-Disordered Breathing: The Sleep Heart Health Study

On Line Supplement

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Detailed Methods

Subjects and Study Design

The Sleep Heart Health Study (SHHS) is a multicenter longitudinal study designed to determine the cardiovascular consequences of SDB. The design and objectives of Sleep Heart Health Study, and detailed descriptions of its member cohorts, protocols, and quality control procedures have been published (1, 2). The Sleep Heart Health Study consists of an ethnically diverse cohort of 6,441 men and women aged >40 years who were members of existing parent cohorts. The Sleep Heart Health Study baseline examination was conducted between December 1995 and January 1998. In 2001-2002, 3295 subjects representing a subset of the original cohort participated in a follow-up exam, including an overnight polysomnogram (PSG). Electrocardiogram (EKG) data for the present analysis were derived from this second PSG, which included lead I bipolar EKG sampled at 250 Hertz, a higher frequency than on the baseline PSG. PSGs were only performed on subjects who were not users of continuous positive airway therapy. Subjects received small non-monetary incentives (e.g. water bottles) for study participation. Regarding the determination of 3,295 participants for the second SHHS exam, there were n=5291 participants with SHHS-2 screening forms, of whom n=3081 completed a sleep study for SHHS-2 data collection with verifiable data. Of participants answering “yes” to “Has a doctor ever told you

that you have sleep apnea?" on the SHHS Screening Form (n=327), n=99 responded "yes" to the question "In the past 3 months, have you slept with a pressure mask ("CPAP" or "BiPAP") for sleep apnea, and were excluded.

Since EKG data collected during the sleep study needed to be reprocessed for this analysis using EKG-specific software, efficiency was optimized by using a nested group-matched exposed and non-exposed design. Subjects were eligible for inclusion in the "exposed" and "non-exposed" groups if their BMI was between 18 and 40 kg/m^2, no use of CPAP was reported, and data were technically satisfactory for the proposed analyses. All "exposed" subjects who met eligibility criteria were included (n=228). Subjects were included in the non-SDB group by selecting subjects who met with eligibility criteria, selecting subjects with a covariate distributions for age (± 2 years), sex, race/ethnicity, and body mass index (BMI, ± $2kg/m^2$) that provided balance with the exposed (SDB) group (n=338) using a SAS macro performing sampling without replacement.(4) Of the 618 subjects who met initial RDI and BMI criteria, 11 were excluded due to lack of technical adequate or complete data and data from 41 participants from the New York center were excluded because the Steering Committee was unable to verify the quality of all data from the follow up examination from that site.

Assuming an arrhythmia prevalence of 10% in the non-SDB group, the study had 88% power to detect a minimum of a 2-fold increase in prevalence. Ethics approval was obtained from the IRB of each site involved with the SHHS examination, and from the Johns Hopkins University Coordinating Center,

Written informed consent for participation in the SHHS was obtained for all individuals.

Statistical Analysis

Analyses were performed using SAS statistical software (SAS Institute Inc., Carey, NC, version 8.2). Arrhythmia subtypes (ventricular, atrial, and conduction delay) were analyzed as dichotomous outcomes (present, absent) with SDB as the relevant exposure; and odds ratios, 95% confidence intervals, and p-values are reported. Multiple logistic regression models included adjusting for age, BMI, sex and coronary heart disease. For complex ventricular ectopy, which occurred at sufficient frequency to allow multivariable adjustments, a hierarchal modeling strategy was used to determine the optimal parsimonious model. Specifically, modeling was performed first with demographic variables, then with addition of cardiovascular disease (CVD) risk factors, and finally with CVD manifestations. Interactions were constructed based upon variables in the final main effects model according to statistical and clinical significance.

Atrial, ventricular, and conduction delay arrhythmias per hour were also analyzed as continuous outcomes. Log-transformed values were used in linear regression models. Model diagnostics, including co-linearity, goodness-of-fit, homoscadasticity, influential observations, were performed.

Sleep Data and Measures

In-home overnight PSG was accomplished with Compumedics ® PS (Melbourne, Australia) equipment. Data were collected on 12 channels and included oximetry (Nonin, MN, Minnesota), heart rate, chest wall and abdominal excursion (by respiratory inductance plethysmography), nasal/oral

airflow (thermistry), body position, electroencephalogram, electrooculogram, chin electromyogram, body position, and lead I EKG. Other data collected by trained technicians included anthropometric data, health data from standardized questionnaires and blood pressure by direct measurement (3). All sleep data were centrally scored at the PSG Reading Center, as described before. The RDI is the number of apneas plus hypopneas per hour of sleep. Apneas were identified if the amplitude of the airflow was absent or almost absent (at least <25% of baseline amplitude) for >10 seconds. Hypopneas were identified if airflow or respiratory effort showed a clear reduction to <70% of baseline for at least 10 seconds, but did not fall so low as to qualify as an apnea. In the analyses reported here, only events that were associated with at least a 3% oxygen desaturation were included, and the RDI included both obstructive (associated with respiratory effort) and central (not associated with respiratory effort) apneas; the latter constituted a median percentage of 2.38% of apneas. The scoring reliability for the RDI was excellent, as reported (5).

Clinical Covariates

Clinical covariate data included: 1.) Demographic variables: age, sex, BMI, race/ethnicity; 2.) Cardiovascular disease (CVD) risk factors: hypertension (based on systolic blood pressure >140 or diastolic >90 or antihypertensive medication use), diabetes mellitus (based on hypoglycemic medication use), cholesterol level, HDL level, smoking status (defined as >20 packs over the past year); and 3.) CVD manifestations: angina, coronary heart disease (composite

variable representing history of myocardial infarction or coronary angioplasty or coronary artery bypass graft surgery), stroke, congestive heart failure, pacemaker placement, and other cardiac surgery. Medication such as antiarrhythmics, nitrates and beta blockers were also considered as covariates in analyses. Covariate data except for lipid profile were ascertained at the time of sleep study acquisition.

Outcome Measures

EKG data were analyzed using software specific for EKG interpretation (Somté®, CompuMedics®). EKG data were manually reviewed by two observers blinded to respiratory events. The number of ventricular ectopic and supraventricular beats was assessed. The estimated intra-class correlation coefficients from a random sample of 20 sleep studies were 0.99 and 0.98 for ventricular ectopic and supraventricular beats respectively, indicating high agreement between the observers. An electrophysiologist reviewed all records with questionable categorization of arrhythmias. Records were first analyzed for artifact defined as increased frequency of activity obscuring the baseline EKG channel precluding valid scoring. EKG data were then scored as supraventricular, ventricular ectopic, or normal beats. P-R interval assessments were made using software-based calipers for atrioventricular block evaluation, and reviewed for second (Type 1 and 2) or third degree patterns. Ventricular arrhythmias identified included: premature ventricular contraction, bigeminy, trigeminy, quadrigeminy, nonsustained ventricular tachycardia (defined as 3 or more consecutive ventricular ectopic beats with an average rate >100 beats per

minute), and a summary variable including all complex ventricular ectopy (i.e. bigeminy, trigeminy, quadrigeminy, or nonsustained ventricular tachycardia). Atrial arrhythmias identified were: premature atrial contraction, supraventricular tachycardia, and atrial fibrillation. Conduction delay arrhythmias were coded as: first, second and third degree atrioventricular block, intraventricular conduction delay and sinus pause (>3 seconds). Arrhythmias were coded as present or absent (for dichotomous outcomes) or as continuous measures (number per hour of sleep).

References.

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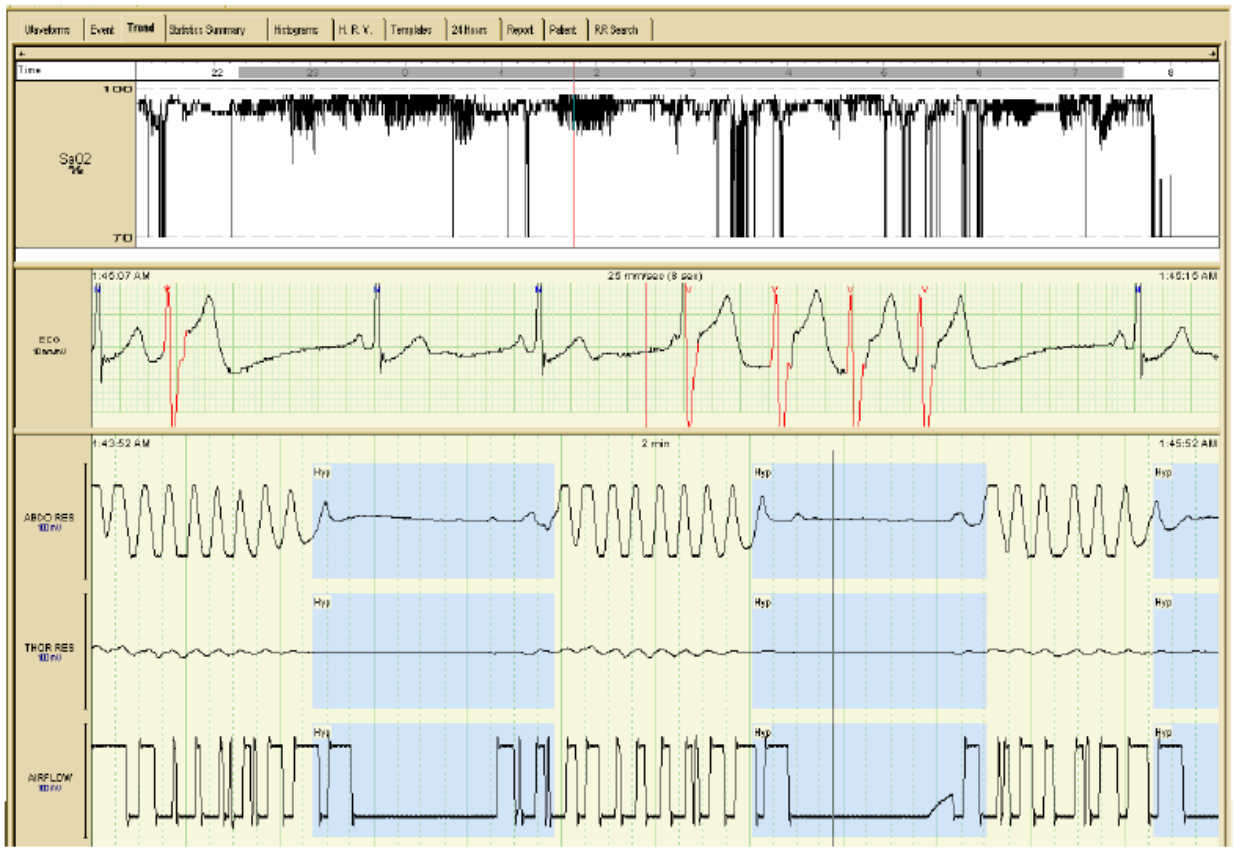
Figure E1. Legend. *Temporal Relationship Between Complex Arrhythmia Occurrence in the Midst of Respiratory Events Accompanied by Oxygen Desaturation.* This is an example from a sleep study of a 61-year old male (Body Mass Index=40.0kg/m2) with an RDI=37.5 events/hour demonstrating the following descending channels: pulse oximetry over the entire night, EKG recording over 8 seconds, abdominal and thoracic inductance, and airflow (the latter three over 3 minutes). The red vertical line in the oximetry data coincides with the red vertical line in the EKG data and the black vertical line in the respiratory parameters. There is an episode of non-sustained ventricular tachycardia occurring in the midst of oxygen desaturation and a respiratory event suggesting the possibility of a temporal relationship.

Figure E 1.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