Association of Nocturnal Cardiac Arrhythmias with Sleep-Disordered Breathing
1. **a. Full Title:** Association of Nocturnal Cardiac Arrhythmias with Sleep-Disordered Breathing  
   **b. Abbreviated Title:** Arrhythmias and SDB

2. **Lead Author:** Reena Mehra MD, Susan Redline; MD, MPH

3. **Timeline:** The target start date is 12/02 and finish date 12/03, assuming P&P approval and Coordinating Center availability for data.

4. **Rationale:** The basis of this study is to determine the relationship between the prevalence of nocturnal arrhythmias and sleep-disordered breathing (SDB).

5. **Hypotheses:** The primary hypothesis contends that the prevalence of nocturnal cardiac arrhythmias is increased in individuals with SDB (respiratory disturbance index \( \text{RDIP3}>30 \)) as opposed to those without SDB \( (\text{RDIP3}<5) \). Secondary hypotheses include:  
   a.) Among the SDB group \( (\text{RDIP3}>30) \), there exists a positive correlation (dose-response relationship) between the prevalence of arrhythmia and degree of sleep disturbances and hypoxemia, as measured by the RDIP3, nocturnal hypoxemia, and sleep fragmentation (the latter as indicated by arousal index),  
   b) SDB will increase risk to a greater extent for ventricular versus atrial arrhythmias,  
   c.) There will be a multiplicative effect between SDB and underlying cardiovascular co-morbidity and diabetes and risk of arrhythmia,  
   d.) Arrhythmias will be most frequent in REM as compared to non-REM sleep.

6. **Data:** The approach is a nested case-control study of the Sleep Heart Health Study-2 (SHHS-2) population. In order to appropriately statistically power the analysis, a total of 500 polysomnography subjects will be evaluated (250 with and 250 without SDB as defined above). Specifically, electrocardiogram (EKG) lead II data at 250 Hertz will be reviewed for cardiac arrhythmias (ventricular arrhythmias, premature atrial contractions, supraventricular tachycardia, sinus pause, asystole and heart block) as determined by the Compumedics® EKG interpretation software package, Somté®. Other variables to be evaluated in the cohort include age, gender, race, body-mass index (BMI), sleep stage, average oxygen saturation, percentage of the tracing with desaturation below 90%, and arousal index; as well as presence of comorbidities such as cardiovascular disease, hypertension, diabetes mellitus, hypercholesterolemia and smoking status. Exclusion criteria are those studies with technically unsatisfactory data, and those with a BMI>34 (to minimize problems with matching). 250 cases \( (\text{RDIP3p}>30) \) will first be randomly identified from the current SHHS-2 database \((>400\ \text{individuals})\). 250 Controls will be identified to achieve group matching (BMI +/--
2 kg/m²; age +/- 2 years; gender +/- 2%). When possible, SHHS2 covariates will be used.

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**SHHS Proposal**

7. **Type of Study:** Mainline Study

8. **Type of Publication:** Journal Article

9. **Analysis Responsibility:** Local (statistics directed by HL Kirchner, PhD). JHU will be asked to generate the list of Ids of cases and matched controls.

10. **Suggested writing group:** Reena Mehra (trainee), Susan Redline (SHHS investigator) and HL Kirchner (statistician) from the RC, and Emelia Benjamin and/or Dan Gottlieb from FHS; others as nominated.
**Association of Nocturnal Cardiac Arrhythmias with Sleep-Disordered Breathing**

**Background and Significance:**

The findings of cardiac arrhythmias in the setting of sleep-disordered breathing (SDB) and improvement with intervention were initially documented in 1977 when Tilkian et al. noted reversal of arrhythmias in patients with SDB subsequent to tracheostomy [1]. Heart rate variability (HRV), sinus arrest, atrioventricular (AV) heart block, ventricular arrhythmias, atrial arrhythmias, and asystole have since been demonstrated in conjunction with apneic events [1-7]. Bradytachyarrhythmias (cyclic HRV) represent perhaps the most common and likely most studied cardiac disturbance associated with respiratory events. Typically, onset of apneas are accompanied by bradycardia with ensuing tachycardia in the post-apneic period in patients with an intact nervous system [8].

The literature regarding the presence of pathologic nocturnal cardiac arrhythmias in SDB is inconsistent, often conflicting, and of questionable validity and reliability due to primarily small sample sizes involved, varying definitions of arrhythmias used, and lack of statistical adjustment for confounding variables. In patients with SDB, wide prevalence ranges of pathological arrhythmias have been observed such as ventricular tachycardia (VT) anywhere from 3-13% in various studies, and premature ventricular contractions (PVC’s) ranging from 20-67% [1, 6, 7]. It is readily apparent, however, that this percentage of PVC’s is notably higher than reported in a multicenter study (ARIC) involving a random population of 15,972 middle-aged adults in which the prevalence of PVC’s was 6% [9].

The existing data regarding atrial arrhythmias in the setting of SDB is relatively sparse consisting mainly of case-reports [2]. In the general population, the prevalence of atrial fibrillation is known to have an age-dependent, dose-response relationship ranging from .8-8.8% from ages 50-89 years old [10]. A male predominance in the incidence of atrial fibrillation per 1000 person years has also been reported [11]. Other types of arrhythmias, such as sinus arrest has been reported in 10% and second-degree AV-block in 5% of a population of 400 patients with obstructive sleep apnea (OSA) [7].

With respect to the prevalence of arrhythmias in general, opposing results have been published in several relatively large studies. Hoffstein and Mateika, in a prospective study, noted a substantial increase in the prevalence of significant cardiac arrhythmias in 458 patients with severe SDB (apnea-hypopnea index (AHI)>10) compared to non-apneic controls [12]. However, Flemons et al., as a result of a prospective study evaluating the prevalence of cardiac arrhythmias in 173 patients with and without SDB, discovered no significant difference between the two groups [13]. It is speculated that the varying
results in these as well as other studies may in part be due to the differing severities of SDB of the study populations as well as inconsistent definitions of arrhythmia [7, 14-16].

**Background and Significance (continued):**

In addition, the issue of the importance of oxygen desaturation in relation to arrhythmias must be considered. In a study of 31 male patients with OSA, Shepard et al found in 16 of 31 patients with an oxygen saturation less than 60%, there was an increase in PVC’s with declining oxygen saturation (p<.01) [14].

Sleep state may impact arrhythmias in SDB. For instance, rapid eye movement (REM) sleep is associated with an even further increase in parasympathetic tone compared to non-REM (NREM) sleep and wakefulness, and is associated with autonomic instability associated with tonic and phasic periods of sleep with the latter accompanied by transient increases in sympathetic tone. It would therefore be reasonable for nocturnal cardiac arrhythmias to be increased during REM sleep periods.

Specific patient populations may be at greater risk for the development of arrhythmias with SDB. For example, gender differences may exist as it has been reported that females with SDB and cardiac disease have a higher heart rate and increased number of PVC’s when compared to their male counterparts (p<.01) [17]. Also, a study of morbidly obese patients (body mass index (BMI)>40), demonstrated an increased incidence of cardiac arrhythmias in patients with severe obstructive sleep apnea (OSA) (AHI>65) and severe oxygen desaturation (SaO2<65%) compared to obese patients with less severe apnea [18]. As would be expected, the presence of cardiac disturbances in the setting of SDB with cardiovascular disease and congestive heart failure (CHF) has also been well established [3, 4, 19, 20].

Although the presence of cardiac arrhythmias, particularly sinus arrhythmia and HRV, are known to occur in the setting of SDB, existing published data are not consistent regarding the relationship of pathological nocturnal cardiac rhythm disturbances with respect to SDB severity as measured by the AHI [1, 6]. Also, the specific relationship of oxygen desaturation, sleep fragmentation, and sleep stage with regard to cardiac arrhythmias in SDB, in addition to interactions observed in various subgroups such as individuals with cardiovascular disease, hypertension, diabetes mellitus, hypercholesterolemia, or those who smoke remains to be adequately elucidated.

**Objectives:**

The primary objective is to determine if the prevalence of nocturnal cardiac arrhythmias are higher among subjects with SDB (RDI3P>30) versus those without SDB (RDI3P<5). The secondary objectives include observing the relationship between nocturnal cardiac arrhythmias and degree of AHI, nocturnal hypoxemia, and sleep fragmentation as indicated by arousal index, as well as overall prevalence of ventricular versus atrial arrhythmias. The interactions of arrhythmias and SDB in subgroups with various
comorbidities such as cardiovascular disease, hypertension, diabetes mellitus, hypercholesterolemia and smoking status will also be analyzed. Sleep stage dependency of arrhythmias also will be assessed.

Methods:

Analytic methods will involve a nested case-control study of Sleep Heart Health Study-2 (SHHS-2) polysomnograms with a software package (Somté®) specific for the interpretation of electrocardiogram (EKG) data provided by CompuMedics® (Abbotsford, Victoria, Australia). The P-series system was used which recorded the following channels: central electroencephalogram, electrooculogram, chin electromyogram, pulse oximeter, chest and abdominal excursion, airflow (by oronasal thermistor), single bipolar EKG (lead II, 250 Hertz), and body position. The SHHS Reading Center (Cleveland, OH) scored all polysomnography recordings using established, standardized methods. Those studies with technically unsatisfactory or uninterpretable data will be excluded.

Subjects (cases and controls) will be identified as follows: Cases: RDI3P ≥ 30; Controls: RDI3P ≤ 5. Controls will be frequency matched to the control group with respect to age (+/- 2 years), gender, race, and BMI (+/- 2kg/m²). All cases with an RDI3P > 30 will be studied with a matched control sample. The following table shows the estimated power of the study under different assumptions of arrhythmia prevalence for the SDB and non-SDB groups. (Table 1.) Calculations are based on the Pearson chi-square test (2-sided), 250 subjects per group and 5% significance level. For example, to detect a 2-fold increase in arrhythmia prevalence, from 10% to 20% (assuming a 20% arrhythmia prevalence in the SDB group versus 10% arrhythmia prevalence in the non-SDB group), with 250 subjects per group and 5% significance level, the study has 88% power. This is equivalent to an odds ratio of 2.25. With a total of 500 subjects we have greater than 80% power to detect an odds ratio of 2.25 for SDB when other covariates have a multiple correlation less than 0.44 with SDB exposure. We propose studying at least 250 individuals in each group to increase the power for logistic regression models and secondary analyses. Additional power may be anticipated for outcomes where all types of arrhythmias are collapsed and for analyses that relate number of arrhythmias to disease severity indices (measured continuously.)

<table>
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<tr>
<th>P_1 (prevalence of arrhythmia among non-SDB)</th>
<th>P_2 (prevalence of arrhythmia among SDB)</th>
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<tbody>
<tr>
<td></td>
<td>0.07</td>
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<tr>
<td>0.05</td>
<td>16%</td>
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<td>0.07</td>
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<td>0.10</td>
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Table 1. Power for Arrhythmia Prevalence Between Non-SDB (P_1) and SDB (P_2) with 250 Subjects per Group and 5% Significance Level
Methods:

For the purposes of this study, we will define pathologic arrhythmias as the following: sinus pauses greater than two seconds, frequent PVC’s, complex ventricular ectopy (bigeminy, polygemin), VT and ventricular fibrillation (VF), frequent premature atrial contractions (PAC’s), supraventricular tachycardia (SVT) exemplified by sudden atrial tachycardia greater than 150 bpm, and AV block (first, second (Types 1 and Mobitz Type 2), and third degree) defined as lengthening of P-R interval and intermittent or persistent loss of P wave and QRS wave association on electrocardiogram (EKG). The specific thresholds (number of PVC’s, etc.) for analysis of dichotomous outcomes will be decided after input from the writing group.

The average oxygen saturation, percentage of study spent below 90% oxygen saturation, stage of sleep when the arrhythmia occurred (REM versus NREM), and arousal index will be assessed. Review of the SHHS-2 population characteristics will also be performed, specifically for age, gender, race, BMI, cardiovascular disease, hypertension, diabetes mellitus, hypercholesterolemia and smoking status.

Analysis:

Statistical analysis will involve logistic regression of the dichotomous exposure variable SDB (present, absent) and dichotomous outcome variable arrhythmia prevalence (present, absent) as defined above. Adjustment for confounding variables such as SHHS-2 site, cardiovascular disease, hypertension, diabetes mellitus, hypercholesterolemia and smoking status will be performed (after also testing for effect modification with restricted analyses). For secondary analyses, analyses will be performed stratified by underlying co-morbidities, age and gender. When appropriate, pooled analyses will be repeated with appropriate interaction terms. Analyses will also be re-run with outcomes specific for atrial versus ventricular arrhythmias. Ordinal logistic regression analyses will be used when the outcome will be classified into several categories of severity (more versus less malignant arrhythmias). Exploratory analyses will also assess whether pattern of arrhythmias varies by sleep stage, or the extent there is a direct correlation between ectopic beats and respiratory disturbances. Calculated p-values of <.05 will be considered statistically significant.

Conclusion:

We propose an important use of SHHS-2 data to evaluate a key unresolved question in the literature: is SDB associated with nocturnal cardiac arrhythmias, and if so, is risk related to level of disrupted sleep or hypoxemia? The results from this study would have serious implications in the realm of diagnostic and therapeutic management strategies for
patients with SDB, particularly as pathologic cardiac arrhythmias likely portend a poorer prognosis and possibly increased risk of sudden death.

**Limitations:**

Estimating magnitude of effect from the current literature is limited. If effects are less than 2-fold and baseline prevalence of exposure is < 10%, power is much limited. Nonetheless, this is the largest population-based dataset available to perform these important analyses.

**References:**
