MS# 1301(SHHS102)

SHHS Proposal

1.  a. Full Title: Temporal Associations Between of Respiratory Disturbances and Cardiac Arrhythmias Occurring During Sleep  
   b. Abbreviated Title: Nocturnal arrhythmias and respiratory disturbances

2.  Lead Author(s): Ken Monahan MD (S Redline and E Shahar SHHS investigators)

3.  Timeline: The target start date is 10/07 and the finish date is 2/08, assuming P&P approval and Coordinating Center availability for data processing.

4.  Rationale: The basis of this study is to characterize the temporal relationship between respiratory disturbances and cardiac arrhythmias.

5.  Hypotheses: The primary hypothesis is that discrete nocturnal cardiac arrhythmias are temporally linked to respiratory disturbances. Exploratory hypotheses include: (a) the temporal link will be most pronounced in REM vs non-REM sleep; (b) the risk of arrhythmia following a given respiratory disturbance will increase with duration of the preceding hypopnea or apnea and its attendant nadir oxygen desaturation.

6.  Data: A sample of sleep studies from the SHHS-2 exam with discrete nocturnal cardiac arrhythmias (atrial fibrillation [AF], non-sustained ventricular tachycardia [NSVT]) and RDI between 2 and 25 events/hour.

7.  Type of Study: Mainline Study

8.  Type of Publication: Journal Article

9.  Analysis Responsibility: Local

10. Suggested writing group: Ken Monahan (trainee), Reena Mehra (faculty member), Sanjay Patel (faculty member), Susan Redline (SHHS investigator), Eyal Shahar (SHHS investigator), Murray Mittleman (statistical consultant), and Amy Storfer-Isser (statistician); others as nominated.

Background and Significance

The relationship between sleep disordered breathing (SDB) and cardiac arrhythmias has been recognized for at least three decades and remains an active area of investigation (Tilkian Am J Med 1977, Zwillich JCI 1982, Guilleminault Am J Card 1983, Hoffstein Chest 1994, Gami Circ 2004, Mehra AJRCCM 2006). SDB increases the risk of incident atrial fibrillation (Gami JACC 2007) and the risk of ventricular
arrhythmias (Shepherd Chest 1985, Fichter Chest 2002), which may explain partially
the increased risk of sudden death during sleeping hours of those with SDB (Gami
NEJM 2005). Proposed mechanisms to explain this relationship have focused on the
contributions to a pro-arrhythmic milieu of apnea-induced hypoxia with subsequent
increases in sympathetic nervous system activity, both acutely and in a tonic fashion

Recently, using data from the Sleep Heart Health Study (SHHS), the prevalences
of atrial fibrillation (AF), non-sustained ventricular tachycardia (NSVT), and complex
ventricular ectopy (CVE – NSVT, bigeminy, trigeminy, quadrigeminy) were shown to be
higher in those with SDB (Respiratory Disturbance Index [RDI] ≥ 30 events/hour) relative
to those with low levels of SDB (RDI < 5 events/hour), even when adjusted for existing
self-reported coronary heart disease and risk factors (Mehra AJRCCM 2006). However,
the prior analysis did not assess the temporal associations between the respiratory
disturbances and cardiac arrhythmias, nor did it examine the role of respiratory
disturbances and concurrent oxygenation status as potential triggers for acute nocturnal
arrhythmias. Additionally that sample was restricted to those with high (RDI ≥ 30
events/hour) and low (RDI < 5 events/hour) levels of SDB and did not evaluate the
association for those with intermediate levels of SDB. Characterizing these associations
is important to promote understanding of potential causal mechanisms and could assist
in designing clinical interventions for reducing cardiac morbidity due to arrhythmias in
patients with SDB.

Objectives

1. To characterize the temporal relationships of respiratory disturbances (apneas and
   hypopneas) and discrete nocturnal cardiac arrhythmias (NSVT, paroxysms of AF) by
   examining the risk of an arrhythmia being associated with a preceding respiratory
disturbance versus being unrelated to such a disturbance.

2. To assess whether or not the temporal relationship between respiratory disturbances
   and arrhythmic events varies based on REM versus NREM sleep.

3. To explore the effects of respiratory disturbance duration and nadir oxygen
desaturation on the risk of discrete nocturnal cardiac arrhythmias (NSVT, paroxysms of
   AF).

Methods

Analytic Sample:
All polysomnograms (PSGs) from the SHHS-2 exam with RDI3p values of 2-25
events/hour with technically satisfactory EKG signals will undergo a Holter type EKG
analysis. All studies in which an arrhythmia occurred will be included in the analysis.

Outcome: Arrhythmia
Given our previous data demonstrating higher odds of AF and NSVT in those
with severe SDB compared to those without SDB, this study will focus on paroxysms of
AF and NSVT as the arrhythmias of interest. Physiological data from the raw EKG
signal will be manually reviewed to identify paroxysmal AF (bursts of atrial fibrillation
preceded by a period of normal sinus rhythm) and NSVT episodes (3 or more
consecutive wide complex beats occurring at a rate of ≥ 120 BPM).
Analytic Approach

To address the hypotheses regarding the temporal association between respiratory disturbances and arrhythmic events, we will use a case-crossover design ([Maclure Am J Epi 1991, Maclure Annu Rev Public Health 2000], which will be done with the assistance of an expert in this type of analysis (Dr Murray Mittleman). This method was designed to analyze the risk of an event occurring in the context of an unusual exposure, with each subject serving as their own control during periods when they are not having an event. In the current application, the 'events' are cardiac arrhythmias (paroxysms of AF and NSVT) and the 'exposures' are respiratory disturbances.

To conduct this analysis, we must operationally define the referent periods and the hazard time. The referent periods are periods of normal baseline risk, while the hazard time is defined as 'a time interval following the onset of a respiratory disturbance when the population experiences an increased risk of an arrhythmia caused by the respiratory disturbance'. We have established an estimate of the hazard time based on prior studies that have examined the effects on physiologic parameters of respiratory disturbances. Respiratory disturbances, such as apnea, lead to oxygen desaturation and increased sympathetic tone. When breathing resumes, sympathetic tone declines, but blood pressure and heart rate increase transiently. Sympathetic nervous system activity, as measured by peroneal nerve MSNA (known to correlate with cardiac norepinephrine levels – [Xie JAP 2001]), increases during apnea ([Luenberger JAP 1995] with mean arterial pressures remaining elevated for ~ 10 seconds after cessation of apnea, even though MSNA activity decreased immediately upon arousal ([Luenberger JAP 1995, Somers JCI 1995]. In normal subjects, systolic blood pressure remains elevated 20-30 seconds after arousal from sleep ([Blasi IEEE 2006]. We also recognize that there is often times a lag between the cessation of a respiratory disturbance and the resultant nadir oxygen saturation level. Therefore, we define the 'physiologic' hazard time for arrhythmia surrounding a respiratory disturbance as the entire respiratory disturbance, the average lag between termination of the respiratory disturbance and the nadir oxygen saturation level, and at least 10 seconds after resolution of hypoxia. We therefore define the hazard period as 90 seconds. To serve as referent periods, we will select randomly 4 epochs of sinus rhythm for each subject; these will be equal in duration to the hazard period and selected from epochs of sleep which are the same as was recorded during the arrhythmic event in order 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' ([Hugonnet AJE 2007], the referent periods will be restricted to those occurring at least 3 hazard periods (4.5 minutes) before the arrhythmia. Since it remains unknown whether or not arrhythmias can affect the prevalence of respiratory disturbances, we will use a unidirectional design; the hazard period and all referent periods will be selected such that they occur prior to the arrhythmia of interest.

**Exposure: Respiratory disturbances**

Preceding each arrhythmia, a hazard period will be identified (see above). In this hazard period, all respiratory disturbances will be identified, including the type of disturbance (central apnea, obstructive apnea or hypopnea); the duration of the apnea or hypopnea, its attendant oxygen nadir desaturation (occurring within 25 seconds of the termination of the apnea or hypopnea) and whether an EEG arousal occurred within 3
seconds of the termination of the apnea and hypopnea. In addition, the sleep stage and epoch time of the occurrences will be recorded.

Other data:
Other data that will be used to describe the sample and to explore effect modification include: the total sleep time, the percentage of the study spent in various stages of sleep (focusing on REM vs NREM), the average oxygen saturation, the percentage of sleep time spent below 90% oxygen saturation, the arousal index and the RDI for the entire study. Sample characteristics including the subject’s age, gender, race, body mass index; history of coronary disease (CAD), hypertension, diabetes mellitus, hypercholesterolemia, smoking status, known arrhythmia from the daytime EKG, use of anti-arrhythmic drugs, and the prior implantation of permanent intra-cardiac devices (pacemakers and/or implantable cardioverter-defibrillators).

Statistical approach
Conditional logistic regression analyses will be used to assess the temporal association between respiratory disturbances and arrhythmic events. For these analyses, the outcome is a binary variable indicating case (arrhythmia) or control (normal sinus rhythm [NSR]) status, and the exposure is a binary variable indicating whether or not the exposure (a respiratory disturbance) occurred within the hazard period. Two analytic approaches will be used to assess whether the relationship between respiratory disturbances and arrhythmic events varies based on REM versus NREM sleep: 1) analyses will be stratified on REM vs. NREM sleep; 2) a two-way interaction between REM status (REM vs NREM) and the exposure will be examined. Exploratory secondary analyses will utilize general estimating equations and frailty indices to model potential differences in recurrent risk across the PSG. Exploratory analyses will consider duration and clustering of respiratory disturbances and their state specific associations. Alternative exploratory models will include as alternative exposures: 1) the nadir oxygen desaturation in the hazard window; 2) whether an arousal occurred in the hazard window.

Primary analyses will use the only one case per record (if more than one arrhythmic event is identified, one will be randomly chosen). However, we will explore methods to utilize more than one case per PSG as well. We will explore potential effect modification by subject characteristics (eg, age, CAD) and PSG characteristics (overall RDI) on the exposure-response relationships.

Power Calculation
We expect ~ 2000 PSGs to have RDI values between 2-25 events/hour. Based on prior work (Mehra AJRCCM 2006), the number of arrhythmic cases (paroxysms of AF or NSVT) to be identified from screening all PSGs that meet this RDI criterion is estimated to be 3% (n = 60). Assuming a median RDI value of 10 events/hour for this subgroup, a respiratory disturbance will occur on average every 6 minutes; with a hazard window of 90 seconds, the probability of a respiratory disturbance (the exposure) preceding a control period of NSR is 25%.
Power: Assuming we will identify 60 cases, each with 3 control periods, we have calculated power for exposure probabilities of 20 and 25% and ORs varying from 2 to 4. Under most assumptions, there is adequate power to detect OR > 2.5.

Power Calculations assuming n = 60 cases, n = 3 control periods per case and \( \alpha = 0.05 \)

<table>
<thead>
<tr>
<th>Power</th>
<th>Odds Ratio</th>
<th>( P_0 )</th>
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<tbody>
<tr>
<td>59.7%</td>
<td>2.0</td>
<td>0.25</td>
</tr>
<tr>
<td>83.9%</td>
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<tr>
<td>94.7%</td>
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<td>0.25</td>
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<tr>
<td>98.5%</td>
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<td>99.6%</td>
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<tr>
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<tr>
<td>99.4%</td>
<td>4.0</td>
<td>0.20</td>
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\( P_0 = \) Probability of Exposure During Control NSR Periods

Conclusions

This study seeks to extend previous SHHS work by evaluating the temporal link between respiratory disturbances and arrhythmias in those with SDB. This investigation could provide insight into mechanisms underlying the well established link between cardiovascular disease and SDB (perhaps modulated partially by the deleterious effects of nocturnal arrhythmias) as well as potentially establish a rationale for the increased rates of nocturnal sudden cardiac death observed in those with SDB. Establishing a link between respiratory and arrhythmic events may also provide an impetus for studying the effects of SDB treatment on nocturnal arrhythmias as well as evidence for a new target for titration of SDB therapies.
REFERENCES


