SHHS Manuscript/Abstract Manuscript Proposal # 1341

1.a. Full Title: Severe Sleep-Disordered Breathing and Incident Atrial Fibrillation: The Sleep Heart Health Study

b. Abbreviated Title [Length, total of 26 letters + spaces]: Severe SDB and Incident AF

2. Lead Author: Yamini S. Levitzky, M.D.

3. Timeline [Target start and finish dates, assuming P&P approval and Coordinating Center availability for central analysis, if applicable]:

   Target start date: 2/1/08
   Analyses completed by: 5/30/08
   Manuscript drafted by: 7/31/08
   Submitted for publication: 9/1/08

4. Rationale:
   Severe sleep-disordered breathing (SDB) is becoming more widely recognized by clinicians as a potential contributor to cardiovascular disease (CVD), as they share many of the same risk factors. It is extremely difficult to study how SDB is related to CVD given the complex inter-relationship with risk factors and physical characteristics (such as BMI) which predispose patients to both diseases. It is unclear whether SDB is related to the development of incident cardiovascular events, specifically atrial fibrillation, in a community-based cohort previously untreated for SDB and without pre-existing AF. We propose here to investigate one aspect of the complex interface between pulmonary and cardiovascular medicine; specifically, how sleep-disordered breathing is related to the development of atrial fibrillation in a community-based sample.

5. Hypotheses:

   We hypothesize that:

   1. Patients in a community-based cohort with severe sleep disordered breathing (defined as a Respiratory Disturbance Index (RDI) >30) will have a significantly greater incidence of atrial fibrillation.
   2. SDB is associated with incident atrial fibrillation independent of body mass index, age, and known CVD.
   3. There may be a relation across strata defined by age, BMI, and presence or absence of CVD.

6. Data [variables, time window, source, inclusions/exclusions]: See Methods section below

7. Type of Study: Mainline study

8. Type of Publication: Journal article

9. Analysis Responsibility: Central analysis
Please attach or include below:

10. **Introduction**

11. **Brief Analysis Plan** [Include list of variables to be used, time frame of data, source of non-SHHS data, and probable statistical method.]

12. **Summary Section**

13. **References**

14. If an ancillary paper, suggested Writing Group members:
   - Susan Redline, MD, MPH
   - Emelia J. Benjamin, MD, ScM
   - Stuart Quan, MD
   - Others as nominated
Introduction

Atrial fibrillation (AF) is among the most prevalent cardiac arrhythmias in the United States and is the source of significant morbidity and mortality.1 The lifetime risk of developing AF over age 40 is approximately 1 in 6 for patients without antecedent myocardial infarction or heart failure, and is responsible for 15-20% of all strokes, underscoring its presence as a major public health issue.2, 3 Numerous risk factors for AF have been identified, including age, obesity, diabetes, hypertension, heart failure, coronary artery disease, and having a parent with AF.4-6

Similarly, obstructive sleep apnea (OSA), a severe form of SDB, shares many of the same risk factors as AF, and has also been associated with increased risk of stroke and death.7 Cross-sectional studies have established that OSA is more prevalent in patients with AF.8 Conversely, there is also a significant increase in prevalence of atrial fibrillation in subjects with severe sleep-disordered breathing (SDB).9 Gami and colleagues conducted a retrospective cohort study of 3542 Olmsted County residents who were referred to sleep clinic due to a suspected sleep disorder, and demonstrated a relation between degree of nocturnal desaturation and risk of incident AF.6 The mechanism of the association between AF and SDB is hypothesized to be related to hypoxemia and autonomic dysregulation leading to arrhythmogenesis, though the precise relation is unclear.10

Previous studies examining SDB have been limited by retrospective design, referral-based samples, and varying definitions and categories (SDB present or absent, RDI >30 vs. <5, or RDI as a continuous variable). To our knowledge, there are no published studies examining incident AF in a community-based sample with untreated SDB. We propose to prospectively examine a cohort of community-based participants who had overnight home PSG to determine whether there is a relation between SDB and incident AF events.

Methods

Participants

The SHHS is an ongoing multi-center, prospective study of 6,441 participants drawn from other cohorts, including: Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Framingham Heart Study, the Strong Heart Study, New York Hypertension Cohorts, Tucson Epidemiologic Study of Airways Obstructive Diseases, and Health and Environment Study, and was originally designed to elucidate the cardiovascular sequelae of SDB.11 To be included, participants had to be age 40 years or older at recruitment and have no co-morbid conditions which would preclude overnight, unattended polysomnography (PSG), such as tracheostomy, or otherwise be treated for OSA already with oxygen or positive airway pressure therapy. All 215 subjects from the New York Hypertension Cohorts were excluded due to poor data quality. In total, 6441 participants were enrolled from 1995-1998, drawn from 11,145 possible participants enrolled the parent cohorts and had overnight PSG. Participants with prevalent AF will be excluded.

Exposure

Overnight PSG was performed using a portable system (PS-2 System; Compumedics Limited, Abbotsford, Victoria, Australia) according to a previously-described protocol.12 Apnea was defined as complete or near complete cessation of airflow (at least <25% of baseline) for more than 10 seconds as detected by thermocouple signal. A hypopneic event was identified by flow or volume of <70% of baseline for greater than 10 seconds, but did not meet criteria for apnea. A Respiratory Disturbance Index (RDI) was calculated as the sum of apnea and hypopnea events with at least a 4% oxyhemoglobin desaturation divided by total sleep time. The RDI has previously been shown to have excellent within-subject
reproducibility as well as intra-observer reproducibility. In summary, the exposure for the proposed project is SDB of severity as characterized by the RDI.

Outcome Ascertainment
The outcome will be incident AF, detected by electrocardiography at SHHS Exam 2 approximately 4 years after the initial PSG. ECGs were centrally processed using the Marcat ECG analysis program, and manually over-read at New York University using the Minnesota Coding system.

Brief Analysis Plan
We are assuming a 3% atrial fibrillation incidence rate and a four-fold difference in outcome events between exposed (RDI4%>25) and unexposed groups (RDI4%<25) (i.e. approximately 0.6% in the unexposed group and 2.4% in the exposed group) based on previous work in the same cohort which demonstrated a four-fold increased odds of AF was noted in fully-adjusted models in a cross-sectional analysis. Follow-up electrocardiograms are available on approximately 3000 participants. We estimate that we will need 685 subjects (137 exposed (RDI4%>25) and 548 unexposed (RDI4%<25) to achieve 80% power with a p-value of <0.05 considered statistically significant.

The exposure, SDB, will be modeled as both continuous (RDI) and categorical variables (RDI low, intermediate, and high; specific criteria for categories to be determined). Logistic regression analyses will be used modeling AF as a dichotomous outcome (present or absent). We will calculate unadjusted odds ratios with 95% confidence intervals. Subsequent models will adjust for covariates including: age, BMI, gender, race, site, and traditional cardiovascular risk factors (hypertension, hyperlipidemia, smoking, and diabetes). Finally, exploratory analyses will stratify by age, BMI, and presence or absence of CVD.

Summary
In summary, we propose to examine a cohort of participants without prevalent AF and without a current diagnosis of sleep-disordered breathing, who were followed for approximately 4 years by the Sleep Heart Health Study to determine whether those with sleep-disordered breathing at increased risk for developing incident AF. We hypothesize that sleep-disordered breathing, through a variety of physiologic mechanisms including hypoxemia and autonomic dysregulation, results in an increased risk of incident AF. This project has potential for broad clinical implications, in that aggressive screening and treatment for SDB may reduce the risk of incident AF events.

References


Reference List


