

ARIC Manuscript Proposal # 2953

PC Reviewed: 3/14/17

Status: _____

Priority: 2

SC Reviewed: _____

Status: _____

Priority: _____

1.a. Full Title: The association of obstructive sleep apnea with ectopy and atrial fibrillation

b. Abbreviated Title (Length 26 characters): Sleep apnea and arrhythmias

2. Writing Group:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **[please confirm with your initials electronically or in writing]**
KG

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Timeline:

Analysis will start as soon as approval is obtained. We plan to complete one manuscript within 12 months from approval of this manuscript proposal.

Rationale:

Obstructive sleep apnea (OSA) involves repetitive upper airway collapse that occurs during sleep, producing an interruption of ventilation that results in subsequent hypoxia, shifts in intrathoracic pressure, and heightened sympathetic activity¹. This common disorder affects between 9% to 38% of the general U.S. population with higher prevalence associated with obesity and advanced age². Prevalence in the overweight and obese is 9% in women and 24% in men. Higher use of healthcare resources and increased risk of cardiovascular morbidity and mortality is reported in patients with OSA compared to patients without OSA³⁻⁵. Cardiovascular diseases that are associated with OSA include stroke⁶, heart failure⁷, coronary heart disease, and cardiac arrhythmias⁸ including premature ventricular contractions (PVC), premature atrial contractions (PAC), and atrial fibrillation (AF) and atrial flutter⁹.

Cardiac arrhythmias affect approximately 14 million U.S. adults and AF, the most common sustained cardiac arrhythmia affects an estimated 2 million U.S adults. Although the prevalence of OSA in AF compared with non-AF cardiology patients has been investigated, studies of OSA with cardiac arrhythmias especially PVCs and PACs are limited. While further study is needed to establish a clear mechanistic link between OSA and cardiac arrhythmias¹⁰, the mechanism likely involves increased intrathoracic pressure, autonomic imbalance, systemic and pulmonary hypertension^{11,12}, intermittent hypoxia, atrial remodeling, and inflammation⁵. These conditions affect structural and electrical remodeling – the substrate for arrhythmias. Studies of OSA and cardiac arrhythmias are limited in the identification of cardiac arrhythmias, as none to our knowledge have used 48-hour continuous Holter monitoring, but rather relied on a single bipolar lead⁸, 12-lead ECG, and/or hospital medical records. Furthermore, several of these studies were conducted during a sleep study. One such study noted the potential for selection bias as the control group patients were identified based on having symptoms suggestive of OSA^{8,9}. These methods for diagnosing cardiac arrhythmias would miss paroxysmal, asymptomatic, and/or intermittent arrhythmias; therefore, our study will contribute information on the association between OSA and cardiac arrhythmias in a community-based population using standardized 48-hour Holter monitoring to detect cardiac arrhythmias.

Main Hypothesis/Study questions:

1. OSA will be associated with presence and burden of PVC and PAC measured by 48-hour Holter monitoring in the ARIC 48-hour ambulatory electrocardiography ancillary study.
2. OSA will be associated with presence and burden of AF measured by 48-hour Holter monitoring in the ARIC 48-hour ambulatory electrocardiography ancillary study.

Study design:

The study population will include African American and White participants from two ARIC sites (Jackson, MS and Forsyth county, NC) who participated in the 48-hour ambulatory electrocardiography ancillary study. Technicians at EPICARE (Wake Forest School of Medicine, Winston Salem, NC) centrally processed the recordings using the GE MARS 8.0.2 (GE, Milwaukee, WI) with a standardized protocol.

Exclusion: Participants with poor quality measures – defined as Holter recordings with >10% noise or <20 hours of Holter recording time. We will also exclude three participants with Holter transmission issues resulting in no Holter recording, and one participant that came to the visit, but chose not to wear a monitor. We will also exclude participants with a paced rhythm on the 48-hour Holter monitor.

Measurements

Outcomes: Burden of PVC, PAC and AF on 48-hour Holter recording.

We will define PAC and PVC separately as:

1. Log of the (total number of PAC/hours of recording time)
2. Log of the (total number of PVC/hours of recording time)
3. Percentage of counts: total number of ectopic beats divided by the total number of beats recorded during the length of Holter monitoring x 100
 - a. % PACs = (number of PACs / number of QRS complexes) x 100
 - b. % PVCs = (number of PVCs / number of QRS complexes) x 100
4. Quartiles and distribution-based cut-point based on the upper 20th percentile of the total counts

We will define AF burden as the percent of time in AF over the 48 hour period. Presence of AF and other cardiac arrhythmias will be evaluated as categorical variables.

Covariates: age, smoking, BMI, race, diabetes, education, study site, use of antiarrhythmic or vasoactive medications, and total cholesterol.

Exposure: We will consider two definitions when defining OSA:

1. Self-reported physician diagnosis of OSA using the AF ancillary study questionnaire conducted at the Holter study visit. Yes to any of these specific

questions will be used to assess self-reported physician diagnosis of OSA.

Question 16: Have you ever used a CPAP or BIPAP machine for sleep apnea, which are breathing machines you wear when sleeping?

Question 17: Have you ever used a mouth piece for sleep apnea that you wear when sleeping?

Question 18: Have you ever had surgery for sleep apnea, called UPPP which is to remove tissue in your throat so the airway is wider?

2. Hospital discharge records with ICD-9-CM code 327.23 (in any position).

Statistical Analysis

We will calculate the means and standard deviations (SD) for the participant characteristics at baseline and stratified by OSA. We will examine the association between prevalence of OSA and presence of PVC, PAC, or AF using logistic regression and we will use multivariable linear regression to examine the association between OSA and burden of PVC, PAC, or AF using inverse variance weighting with weights that account for the study's complex sampling design and non-response. Models will be adjusted for confounders - age, smoking, BMI, race, education, study site, diabetes, use of antiarrhythmic or vasoactive medications, and total cholesterol.

**7.a. Will the data be used for non-CVD analysis in this manuscript? ___ Yes
X No**

**b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? _____
Yes ___ No**

(This file ICTDER03 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

**8.a. Will the DNA data be used in this manuscript? _____ Yes X
No**

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
_____ Yes _____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under

the Study Members Area of the web site at:
<http://www.csc.unc.edu/ARIC/search.php>

Yes No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

MP	Year	Title, Lead
2705	2015	The race specific prevalence of atrial fibrillation with 48 hour ambulatory electrocardiography: The ARIC study – Laura Loehr
2665	2015	Repeatability of ectopic beats from 48 hour ambulatory electrocardiography: The ARIC study– Michelle Meyer
2199	2013	Sleep Disordered Breathing, Sleep Duration and the Risk of Incident Self-Reported Diabetes: the Atherosclerosis Risk in Communities Study - Mako Nagayoshi
2754	2016	The Combined Effect of Diabetes and Sleep Apnea on Incident Cardiovascular Disease and Mortality in a Community Cohort - R. Nisha Aurora

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes

No

11.b. If yes, is the proposal

A. primarily the result of an ancillary study (list number* 2012.08)

B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____)

*ancillary studies are listed by number at <http://www.csc.unc.edu/aric/forms/>

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from <http://publicaccess.nih.gov/> are posted in <http://www.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms.

http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed Central

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