ARIC Manuscript Proposal #2220

1. **Full Title:** Morphological and functional cardiac changes associated with obstructive sleep apnea

   **b. Abbreviated Title (Length 26 characters):** OSA, echocardiography, and cardiovascular outcomes in the community

2. **Writing Group:**
   Gabriela Querejeta, Susan Redline, Scott D. Solomon, Amil M Shah. *Others Welcome*

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

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3. **Timeline:** Analysis will begin once final Visit 5 echocardiographic data and necessary covariate data is available. We anticipate a manuscript completion in approximately the following 6 months (April 2014).

4. **Rationale:**
Obstructive sleep apnea (OSA) affects at least 2-6% of the U.S. population and is associated with multiple cardiovascular (CV) co-morbidities, including systemic hypertension, the metabolic syndrome, stroke, atrial arrhythmias, and pulmonary hypertension. OSA has been associated with coronary heart disease (CHD), heart failure (HF), stroke, and death. OSA is characterized by repetitive episodes of nocturnal hypoxemia, with associated sympathetic activation, hypertension, and tachycardia. The nocturnal hypoxemia likely contributes to ischemia, as supported by several publications demonstrating ECG changes consistent with ischemia occurring in association with apneas, although this finding has not been universal. OSA may also cause myocardial stress and injury due to the increased load on both the right and left ventricles resulting from marked swings in intra-thoracic pressure during obstructed breathing, as well as associated paroxysmal nocturnal and more chronic systemic and pulmonary hypertension. Additionally left ventricular systolic and diastolic function have been shown to be impaired in association with OSA and to improve with treatment with CPAP, however the degree to which these findings are confounded by co-morbidities remains unclear. In addition, OSA has also been associated with a higher arterial stiffness independently of cardiovascular risk factors.

Due to the association of OSA with cardiovascular risk factors such as male gender, age, pulmonary, and systemic hypertension, smoking, and obesity, determining the independent association of OSA with abnormalities of cardiac structure and function has been challenging. While some studies have identified an association between OSA and cardiac remodeling independent of potential confounders, these findings have not been universal. In addition, the association of long-term exposition to OSA with abnormalities of cardiac structure and function has not yet been described.

Echocardiography at Visit 5 among 1,920 ARIC subjects who underwent polysomnography in 1995-1998 as part of the Sleep Heart Health Study, offers a unique opportunity to address these gaps in our knowledge of the cardiovascular impact of OSA. Specifically we aim to study the association of OSA severity, based on the respiratory disturbance index (RDI), with echocardiographic measures of (1) left ventricle structure and function, (2) pulmonary vascular and right ventricle function, and (3) arterial stiffness.

5. Main Hypothesis/Study Questions:
We hypothesize that,
(1) Compared to those without OSA, participants with prevalent OSA in 1995-1998 (SHHS visit) will demonstrate greater LV remodeling, LV systolic and diastolic impairment, pulmonary hypertension, pulmonary vascular dysfunction, and RV dysfunction independent of other cardiovascular risk factors.
(2) Participants with OSA at SHHS visit who do not report subsequent treatment for OSA will demonstrate more pronounced perturbations of cardiac structure and function than those who do report treatment, while those who do report treatment will demonstrate greater perturbations than those never diagnosed with OSA.
(3) Compared to those without OSA, participants with prevalent OSA in 1995-1998 (SHHS visit) will demonstrate greater arterial stiffness independent of other cardiovascular risk factors.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study Design
We will determine the association between OSA presence and severity assessed at SHHS visit (1995-1998), with measurements of cardiac structure and function and vascular function at Visit 5.

Inclusion/Exclusion Criteria
The analysis population will include ARIC participants in visit 5 who were included in the SHHS and measured OSA status by polysomnography between 1995-1998 and were free of established heart failure or coronary heart disease at either the SHHS visit or the ARIC visit 4. Patients with incident myocardial infarcts or heart failure will also be excluded. Patients reporting a new diagnosis of OSA during the follow-up period will also be excluded from this analysis.

Variables of Interest

Exposure variables:
(1) From the primary analysis, OSA group will be based on RDI measured between 1995-1998. Groups will be defined by RDI by conventional clinical categories: non-OSA (RDI<5) mild (RDI≥5-<15), moderate (RDI ≥15-<30) and severe (RDI>20).
(2) For the secondary analysis, we will use nighttime hypoxemia as measured by the percentage of sleep-time with oxygen saturation lower than 90% (PCTLT90). Population will be divided in groups by tertiles based on PCTLT90 population’s distribution.

Outcome variables:
(1) Echocardiographic measurements of LV structure and function: LV end-diastolic and end-systolic dimensions and volumes, LV wall thickness, LVEF, tissue Doppler systolic and diastolic velocities, E/A ratio, left atrial size, and LV deformation.
(2) Echocardiographic measurements of RV size and function, pulmonary artery systolic pressure, and pulmonary vascular resistance.
(3) Measurements of arterial stiffness (pulse wave velocity).

Covariates of interest:
1) Self-reported OSA and self-reported use of CPAP at ARIC visit 5.

2) Demographic and clinical variables including age, gender, BMI, and kidney function (eGFR). Analysis will also be performed with additional adjustment for potential causal intermediaries, including hypertension, diabetes, smoking status and dyslipidemia. All covariate values will be drawn from ARIC Visit 4.

3) Change over time (between ARIC visit 4 and visit 5) in clinical variables including incident atrial fibrillation, hypertension, diabetes mellitus, kidney function as well as change in blood pressure, BMI, eGFR and BMI.

Summary of Data Analysis

To address the hypothesis in a first approach: (1) we will study echocardiographic measurements compared between a) people that have not OSA based on polysomnography at SHHS-ARIC visit 4 and report to not have OSA at visit 5; b) people who have not OSA based on polysomnography at SHHS-ARIC visit 4 and report to have OSA at visit 5; b) people found to have OSA at SHHS-ARIC visit 4 using ANOVA analysis. And (2) we will compared the cardiac morphology and function comparing between all 4 OSA groups using a p for trend analysis. The association will also be studied after multivariable adjustment for self-reported OSA and use of CPAP as well as potential confounders/intermediaries measured at the baseline time and changes over time of these variables.

A secondary analysis will be repeated studying the association with tertiles of PCTLT90% as a measure of night-time hypoxemia due to OSA severity.

Limitations:

Our aim is to associate cardiac abnormalities measured by echocardiography 12 years after the assessment of their OSA status. The main limitation of this analysis is incomplete data regarding incident OSA and timing, status, and compliance with OSA therapy. OSA status (including treatment for OSA) at Visit 5 is assessed by questionnaire, although the validity of this metric is unclear. Similarly, despite adjusting for baseline potential confounders as well as changes in those confounders between ARIC visit 4 and visit 5, we cannot exclude the possibility of residual confounding due both to risk factors and progression of risk factors between visits.

7.a. Will the data be used for non-CVD analysis in this manuscript? _____ Yes _____ 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 _____ 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.cscce.unc.edu/ARIC/search.php

____ X____ 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)?

MS#574S- (Benjamin, EJ et al) “Left heart morphology and systolic function in sleep-disorder breathing”.

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

____ X____ Yes  ____ No

11.b. If yes, is the proposal

____ X____ A. primarily the result of an ancillary study (list number* 1995.12 and 2008.10)  

____ 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.cscc.unc.edu/aric/forms/

12. 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.

References:


26 Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newmann AB, Lebowitz MD, Pickering TG. Association of sleep-disordered breathing,


