ARIC Manuscript Proposal #2462

PC Reviewed: 11/11/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Smoking and Cardiac Structure and Function in an Elderly Cohort.

b. Abbreviated Title (Length 26 characters): Smoking and cardiac structure and function.

2. Writing Group:
Writing group members: Wilson Nadruz Junior, Alexandra Gonçalves, Brian Claggett, Gabriela Querejeta Roca, Amil Shah, Susan Cheng, Dalane Kitzman, Scott D. Solomon, others welcome

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

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3. Timeline: Analysis will begin following proposal approval with the aim of completing analysis and a manuscript within 6 months.

4. Rationale:

Heart failure (HF) is a disorder afflicting 5 million Americans, with over 80% of HF hospitalizations occurring in elderly people[1]. If current trends continue, 6 million of Americans aged >65 years will have HF by 2030[2]. Up to half of HF cases occur in the setting of preserved left ventricular ejection fraction, a syndrome which accounts for substantial mortality, ranging from 10-30% annually and for which no proven therapies are currently available[3,4].

Cigarette smoking has been associated with incident HF, even after adjustment for coronary heart disease[5,6]. Some reports have also suggested that smoking might exert effects on cardiac structure and function. For instance, population-base studies showed that smoking was related to worse left ventricular (LV) function and higher LV mass in individuals without overt coronary heart disease[7,8,9,10]. Conversely, the effects of tobacco on LV geometry are uncertain, given that controversial data regarding the impact of smoking on wall thickness and chamber volume have been reported[9]. The mechanisms by which smoking leads to cardiac remodeling and dysfunction are not established but may include neurohormonal changes, oxidative stress, and inflammation[6,11]. Other potential mechanism includes increases in arterial load imposed to the heart. This hypothesis seems particularly attractive in elderly subjects, who have been reported to exhibit higher blood pressure levels in association with tobacco smoking[12,13]. In this regard, evaluation of the effects of smoking not only on blood pressure, but also on arterial elastance, a measure of total arterial load that incorporates both mean and pulsatile components[14], and on ventricular-arterial coupling might contribute to explain the mechanisms underlying the association between tobacco and LV dysfunction and remodeling.

The relationship between smoking and cardiac structure and function, particularly myocardial deformation, has not been previously described in a large elderly population without overt coronary heart disease. The ARIC study represents an ideal opportunity to address this issue and to evaluate potential mechanisms involved in this regard.

5. Main Hypothesis/Study Questions:

Current and former smoking at Visit 5 will be associated with higher LV mass and worse systolic and diastolic function and these alterations will be more pronounced in current smokers.

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 and Inclusion/Exclusion Criteria:

We will perform a cross-sectional analysis of smoking status and echocardiography parameters obtained during Visit 5. The study sample will include all patients who underwent echocardiography during Visit 5 (2011-2013) with images of acceptable quality for analysis. For the analysis, those with coronary heart disease, severe valvular disease, chronic obstructive pulmonary disease, who were neither White nor African American and with missing smoking data at Visit 5 will be excluded.

Variables to be evaluated

Exposures variables:

1) Categorize participants into 3 groups based on smoking status at Visit 5:
    a. Current smokers
    b. Former smokers
    c. Never smokers

2) Pack-years (We will calculate the pack-years of smoking using self-reported data collected from Visit 1 to Visit 4. At visit 5, this variable was not collected; however, a proxy "pack-years" measure at Visit 5 will use the last reported (at Visit 4) quantity of cigarettes smoked per day as the "pack" and the number of times the subject responded to the question `Do you smoke?´ on the follow up interview as the "years")

Outcome variables:

1) Echocardiographic variables (Visit 5 echo) of LV structure (LV end-diastolic and end-systolic volumes and dimensions), wall thickness, relative wall thickness, and mass), LV diastolic function (E wave, A wave, E wave deceleration time, TDI E', and LAVi), LV systolic function (LVEF, mid-wall fractional shortening, longitudinal strain, circumferential strain), pulmonary hemodynamics (estimated PASP based on TR jet velocity, PVR), and right ventricular function (RVFAC, TDI tricuspid annular S') and arterial-ventricular coupling (arterial elastance and end-systolic LV elastance).
2) Biomarkers of cardiac remodeling (NT-proBNP and high sensitivity troponin T) at Visit 5.

Potential covariates:

Demographic characteristics (age, race, sex, body mass index, socioeconomic status), cardiovascular risk factors (diabetes, arterial hypertension, dislipidemia, family history of heart failure, alcohol consumption), blood pressure, use of antihypertensive medications or statins, plasma lipid levels (i.e. HDL and LDL cholesterol, triglycerides), C-reactive Protein, creatinine clearance.

Analytical approach:

Continuous normally distributed data will be displayed as mean and standard deviation and continuous non-normally distributed data will be displayed as median and interquartile range. Categorical data will be reported as percent frequencies and compared by chi-squared or Fischer exact tests. Continuous data will be compared by Wilcoxon rank sum test, t test, Kruskall-Wallis test and 1-way ANOVA followed by Bonferroni test as appropriate. Associations between smoking status and cardiac variables will be evaluated using linear regression and multivariable logistic regression analyses adjusting for the significant covariates. NT-proBNP will be modeled continuously using log transformed values, while hsTroponin-T will be modeled as an ordinal categorical variable using five categories. The relationship between pack-years of smoking and cardiac variables will be assessed in the whole sample as well as in current and former smokers. P values<0.05 will be considered significant.

Limitations:

A limitation of the cross-sectional design will be the inability to make conclusions about causality. Conversely, smoking status is a self-reported variable, which may result in recall bias. Additionally, in evaluating Visit 5 patients, there is a survival bias as they may represent a healthier population.

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.cscc.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)?

Smoking History and Preclinical Change in Echocardiographic Defined Cardiac Structure and Function: The ARIC Study. #949

Relationship between pulmonary airflow obstruction, cardiac structure and function, and heart failure risk in a biracial elderly cohort: The ARIC study. #2117

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?
____ Yes __X__ No

11.b. If yes, is the proposal

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

___ 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/

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.cscc.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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