ARIC Manuscript Proposal #3750

PC Reviewed: 12/8/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of Left Atrial Function with Neurocognitive Outcomes in the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS)

b. Abbreviated Title (Length 26 characters): **LA function and cognition**

2. Writing Group: Wendy Wang, Michael Zhang, Riccardo Inciardi, Faye L. Norby, Michelle C. Johansen, Romil Parikh, Amil M. Shah, Alvaro Alonso, Elsayed Z. Soliman, Thomas H. Mosley, Rebecca F. Gottesman, Scott D. Solomon, Lin Yee Chen

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

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3. Timeline:
Data analysis to begin immediately; pen draft expected spring/summer 2021.

4. Rationale:

Lower left atrial (LA) function is associated with cardiovascular disease in the general population and worse outcomes among those with cardiovascular disease.[1] Reduced LA emptying fraction is associated with cardiovascular events, such as atrial fibrillation, ischemic cerebrovascular events, and death.[2–5] In addition, LA emptying fraction has been reported to provide prognostic information over and above LA volume index,[3–5] such as in predicting incident atrial fibrillation or cardiovascular events.[4,5]

To our knowledge, no prior studies have assessed whether reduced LA function is associated with cognitive decline or incident dementia. However, based on previous research, this link may be plausible. ECG markers of left atrial abnormality have been found to be associated with vascular brain injury, cognitive decline, and dementia in prospective community-based cohorts.[6–8] Additionally, reduced LA reservoir function is cross-sectionally associated with presence of silent brain infarcts and white matter hyperintensities,[9] which may both eventually lead to cognitive impairment and/or dementia.[10]

The ARIC study is well suited to assess the knowledge gap regarding the relationship between LA function measures and neurocognitive outcomes. At visit 5 (2011-13), 2D-echocardiograms with speckle tracking was performed, which enabled the measurement of LA function by strain analysis (Chen, 2015.29). Therefore, in this project, we aim to evaluate the prospective association of LA function measures with cognitive decline and incident dementia.

5. Main Hypothesis/Study Questions:

Aim: To evaluate the prospective associations between measures of LA function at visit 5 with cognitive decline and incident dementia after visit 5

We hypothesize that those with reduced LA function will have greater cognitive decline and greater incidence of dementia.

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).

<u>Study design:</u>

Prospective cohort from visit 5 to most recent data available.

<u>Inclusion/Exclusion:</u>

Participants who had echo measurements done at visit 5 will be included in this analysis. We will exclude those with prevalent dementia at visit 5 and missing LA function data. Those whose race was other than black or white will be excluded, as well as blacks from the MN and MD centers. We will also exclude those with missing covariates. For the cognitive decline analysis, we will exclude those with missing baseline cognitive data (visit 5) and those who scored below the 5th percentile on any cognitive test at visit 5.

Variables

Exposure: The following LA function measures (obtained at visit 5) will be assessed continuously (per 1-SD)

1. LA reservoir strain (will also be assessed categorically with <28.2 as the cutoff for reduced LA reservoir function)
2. LA contractile strain
3. LA conduit strain
4. LA emptying fraction
5. LA passive emptying fraction
6. LA active emptying fraction

Primary outcome:

1. Cognitive decline from visit 5 to visit 7: changes from visit 5 to visit 7 in domain factor scores of memory, executive function, and language, as well as a global cognitive score will be used to assess cognitive decline, as done previously.[11] The composition of each domain is as follows:
   - Memory: delayed word recall test, logical memory, incidental learning
   - Language: word fluency test, animal naming, Boston naming
   - Executive function: digit symbol substitution test, digit span backwards, trail making tests (parts A and B)

2. Dementia events after visit 5: Adjudicated dementia events as previously identified in ARIC will be used.[12] Level 3 dementia diagnosis will be used for all analyses.
   - Level 1 includes adjudicated outcomes from visits 6 and 7 NCS evaluations, including evidence of cognitive decline based on assessments from prior visits.
   - Level 2 includes cases identified in level 1, as well as participants who did not attend NCS visits, but had their cognitive status evaluated through a validated phone-based cognitive assessment interview.
   - Level 3 includes level 1 and 2 cases, as well as participants identified through surveillance for hospitalization discharge codes (ICD-9) or death certificate codes related to dementia.

Other confounders/covariates (obtained from visit 5): age, sex, race/center, education (from visit 1), APOE ε4, body mass index (BMI), smoking status, diabetes, hypertension, stroke, coronary heart disease, heart failure, atrial fibrillation, LA volume index, left ventricular (LV) ejection fraction, LV mass index, use of anticoagulants

Statistical analysis

- Baseline characteristics will be described using mean ± SD for continuous variables and proportions for categorical variables.
- Dementia incidence after visit 5 will be calculated, stratified by LA reservoir function.
- Linear regression models with generalized estimating equations will be used to assess the association between LA function measures with cognitive decline. Robust variance and an unstructured correlation matrix will be used. To address selection bias and attrition, we will

incorporate inverse probability weighting to account for attrition due to death or visit non-attendance.
- Cox proportional hazards models will be used to assess the relationship between LA function with incident dementia (level 3 cases).
- Interactions by age (median split), sex, race, and APOE ε4 will be explored. Stratified models will be reported when appropriate.
- For all analyses, the following models will be used:
  - Model 1 will be adjusted for age, sex, race/center, education, APOE ε4
  - Model 2 will be adjusted for model 1 plus BMI, smoking status, diabetes, hypertension, stroke, coronary heart disease, heart failure, atrial fibrillation, use of anticoagulants
  - Model 3 will be adjusted for model 2 plus LA volume index
  - Model 4 will be adjusted for model 3 plus LV ejection fraction, LV mass index
- As stroke may be on the causal pathway between LA function and dementia, we will include a model that additionally adjusts for time-dependent incident stroke after visit 5 to determine whether interim stroke explains the possible association of lower LA function with cognitive decline and dementia.
- The following sensitivity analyses will be performed:
  - Exclude participants with prevalent AF at visit 5.
  - Exclude participants with prevalent stroke at visit 5 or incident stroke between visit 5 and 7.

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 ICTDER 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? __x__ 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"? __x__ 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/mantrack/maintain/search/dtSearch.html

___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)?

#2546: LA enlargement, cognition, and dementia (Zhang)

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* _2008.06 (NCS), 2015.29_)

___ 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 https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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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