ARIC Manuscript Proposal #3915

PC Reviewed: 8/10/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of Left Atrial Function and Size with Longitudinal Change in Brain Morphology—Implications for Dementia Prevention: the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS)

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

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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 within 6-9 months.

4. Rationale:

Previous studies have reported that atrial fibrillation (AF) and clinical ischemic stroke are associated with an increased risk of dementia.[1–3] Recent evidence indicates that atrial myopathy, which is characterized by left atrial (LA) dysfunction and enlargement, is also associated with elevated dementia risk, independent of AF and stroke. Currently, reasons for this association are unclear and may include vascular brain injury.

The Cardiovascular Abnormalities and Brain Lesions (CABL) study found that reduced LA reservoir function is associated with silent brain infarcts and greater white matter hyperintensity (WMH) volume.[4] Additionally, greater LA minimal volume index, but not LA maximal volume index, was associated with subclinical cerebrovascular disease.[4] More recently, the CABL study reports that LA strain measures are independently associated with silent brain infarcts, but not with WMH volume.[5] However, both of these studies consisted of small sample sizes (n=455 and 270, respectively).[4,5] In addition, ECG markers of atrial myopathy have been found to be associated with vascular brain injury. The Cardiovascular Heart Study (CHS) reports that higher $PTFV_1$ was associated with more prevalent infarcts and greater baseline white matter grade.[6] In participants who had two brain MRI scans (n=1839), elevated $PTFV_1$ was associated with worsening white matter grade, but not with incident infarcts.[6]

Critical knowledge gaps remain. Notably, although prior studies have characterized the neuroimaging correlates of atrial myopathy, the extent to which markers of vascular brain injury explain the association of atrial myopathy with dementia risk has not been studied. Therefore, we propose to examine two aims: 1) assess the association of LA function and size with vascular brain injury, accounting for AF, 2) evaluate the longitudinal changes in brain MRI findings and 3) quantity the extent to which these associations explain the relationship of atrial myopathy to dementia.

5. Main Hypothesis/Study Questions:

Aim 1: Evaluate the cross-sectional association between LA function and size at visit 5 and brain MRI measures at visit 5

Hypothesis: Participants with lower LA function and greater LA size will have more neuroimaging markers of vascular brain injury (infarcts, microbleeds, and greater WMH volume) and smaller regional brain volumes.

Aim 2: Evaluate the prospective association between LA function and size at visit 5 and longitudinal change in brain MRI findings (visit 5 to visit 6/7)

Hypothesis: Participants with lower LA function and greater LA size at visit 5 will have higher odds of increased markers of vascular brain injury (new infarcts and microbleeds, worsening WMH volume) and greater longitudinal decrease in regional brain volumes.

Aim 3: Evaluate the prospective association of LA function and size at visit 5 with incident dementia, accounting for longitudinal change in markers of vascular brain injury

Hypothesis: Participants with lower LA function and greater LA size at visit 5 will have higher incidence of dementia, independent of AF. From mediation analysis, this association will be largely mediated by new silent brain infarcts between visit 5 and visit 6/7.

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:
Aim 1: Cross-sectional at visit 5
Aim 2 and 3: Prospective from visit 5 to visit 6/7

Inclusion/Exclusion:
Participants who had echo measurements and brain MRIs done at visit 5 will be included in this analysis. We will exclude participants with prevalent dementia or prevalent stroke at visit 5 and those with missing covariates. Those whose race was other than Black or white will be excluded, as well as Black participants from the MN and MD centers due to low numbers.

Variables

Exposure: The following LA measures (obtained at visit 5) will be assessed continuously

LA function measures (per 1-SD decrease)

1. LA reservoir strain
2. LA contractile strain
3. LA conduit strain
4. LA emptying fraction
5. LA passive emptying fraction
6. LA active emptying fraction

LA size measures (per 1-SD increase)

1. LA maximal volume index
2. LA minimal volume index

Primary outcome:

Aim 1: The following brain MRI measures (obtained at visit 5) will be assessed

1. WMH volume
2. Presence or absence of infarcts and microbleeds (binary variables)
   - Any infarcts
   - Lacunar infarcts
   - Cortical infarcts
   - Any microbleeds
   - Subcortical microbleeds
   - Lobar microbleeds
3. Brain region of interest (ROI) volumes
   - Deep gray matter volume
   - Temporal lobe volume meta ROI

Aim 2:

1. Increase in number of brain infarcts

2. Increase in number of cerebral microbleeds
3. Increase in WMH volume
4. Decrease in regional brain volumes
    - Deep gray matter volume
    - Temporal lobe volume meta ROI

Aim 3:

- Dementia events after visit 5 (through 2019 or latest available data); 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.
- For mediation analysis, we will assess whether markers of vascular brain injury (change in number of infarcts, microbleeds, WMH volume) mediate the association between LA function or size and dementia.

Other confounders/covariates (obtained from visit 5): age, sex, race/center, education (from visit 1), APOE ε4, body mass index (BMI), smoking status, systolic blood pressure, antihypertensive medications, diabetes, atrial fibrillation, coronary heart disease, heart failure, anticoagulant use, total intracranial volume, left ventricular (LV) mass index, LV ejection fraction, total intracranial volume

Statistical analysis

- Baseline characteristics will be described using mean ± SD for continuous variables and proportions for categorical variables.
- Aim 1:
    - Linear regressions will be used for continuous outcomes (WMH volume and brain volume measures), while logistic regression will be used for dichotomous outcomes (infarcts and microbleeds).
    - Each brain volume will be scaled based on their standard deviations in order to compare the magnitude of association across brain regions.
    - Because WMH is highly skewed, it will be log base 2 transformed for normality.
- Aim 2:
    - Poisson regressions will be used for count outcomes (number of infarcts or microbleeds).
    - Linear regressions will be used for brain volume loss.
    - Analyses will incorporate weights to account for attrition due to death or visit non-attendance.
- Aim 3:

- Cox proportional hazards model will be used to assess the relationship between LA function and size with incident dementia (level 3 cases).
- Mediation analysis[7] will be used to quantify the extent to which the associations between LA measures and dementia are mediated by markers of vascular brain injury.
- If dementia is diagnosed before the visit 6/7 brain MRI scan, participants will be censored.

- For all analyses, the following models will be used:
  - Model 1 will adjust for age, sex, race/center, education, APOE ε4, total intracranial volume (for volume outcomes only)
  - Model 2 will further adjust for systolic blood pressure, antihypertensive medications, BMI, diabetes, smoking status, coronary heart disease, heart failure, atrial fibrillation, anticoagulant use
  - Model 3 will further adjust for LA volume index (for LA function measures only), LV ejection fraction, LV mass index
- Interactions by age (median split), sex, race, and APOE ε4 will be explored. Stratified results will be reported when appropriate.
- We will conduct the following sensitivity analyses:
  - Exclude participants with prevalent atrial fibrillation at visit 5
  - Aim 2: exclude participants with prevalent infarcts and microbleeds when assessing incident infarcts and microbleeds
- All analyses will incorporate weights for selection into the brain MRI study.

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)?

#3750: LA function and cognition (Wang)

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* __2008.05 (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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