ARIC Manuscript Proposal #4220

PC Reviewed: 03/14/23 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Association of Left Atrial Function with Frailty in Older Adults: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): LA Function & Frailty

2. Writing Group:

Writing group members: Daokun Sun, Romil R. Parikh, Wendy Wang, Anne Eaton, Pamela L. Lutsey, B. Gwen Windham, Riccardo M. Inciardi, Scott D. Solomon, Amil M. Shah, Lin Yee Chen, and others welcome

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

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3. Timeline: Data analysis to begin immediately, anticipated draft completion Summer/Fall 2023.

4. Rationale:

Left atrial (LA) myopathy, characterized by abnormalities in function and size of the left atrium, is associated with adverse cardiovascular outcomes. Increased LA size is an established risk factor for atrial fibrillation, heart failure, and ischemic stroke. Additionally, recent studies suggest that functional changes in the left atrium are also associated with multiple cardiovascular disease outcomes independent of LA size.[1–4]

Left atrial strain, measured by two-dimensional speckle-tracking echocardiography, is a useful and reproducible parameter for the assessment of LA function and LA myocardial deformation. Recent studies have demonstrated the importance and potential clinical application of LA strain to improve diagnosis and evaluation of cardiovascular disease outcomes. In the Copenhagen City Heart Study, Hauser et al. found that the incidence rate of atrial fibrillation in people with peak atrial longitudinal strain < 32% is more than 5 times greater than those with peak atrial longitudinal strain > 41%.[5] Reduced LA strain is also linked with increased left ventricular filling pressure and heart failure.[6,7] In a study among community-dwelling older adults, Potter and coauthors reported that a LA reservoir strain < 24% is associated with nearly 2 times greater risk of incident heart failure after adjusting for confounders.[8] In addition, lower LA function is associated with incident dementia.[2]

Frailty is a multifactorial metric to describe increased vulnerability to compromised outcomes following stressor events.[9] The status of frailty is commonly seen in older adults and can be highly prevalent in people with cardiovascular diseases such as atrial fibrillation and heart failure. Prior studies have shown that the risk of frailty can be 6 times greater in people with heart failure and the prevalence of frailty in people with atrial fibrillation can be up to 75%.[10–12] Frail people with heart failure and/or atrial fibrillation have remarkably increased risk of hospitalization, reduced quality of life, and mortality.[13] Therefore, early identification of people at high risk of frailty is of critical importance.

Current literature suggests that LA size is an independent predictor of frailty.[14,15] However, it is not clear whether reduced LA function may also be a risk factor for frailty independent of prevalent cardiovascular conditions and dementia. In this study, we will investigate the association between LA function, measured by LA strain, and incident frailty in older adults.

5. Main Hypothesis/Study Questions:

Lower left atrial (LA) function is associated with increased risk of frailty, independent of cardiovascular conditions and 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).

Study Design

Prospective cohort study from Visit 5 to 7.

Inclusion/Exclusion

The ARIC visit 5 will be used as the baseline. We will include participants with left atrial function measured by echocardiogram at visit 5. Participants with prevalent frailty at visit 5 will be excluded, as well as those who are neither African American nor white, and African Americans from the MN and MD centers. We will also exclude participants whose frailty status

were not evaluated at either visit 6 or visit 7, for whom we lack their information of frailty status after visit 5.

Variables

Exposures: Left atrial (LA) strain measured on two-dimensional speckle-tracking echocardiography at Visit 5, including 1. LA reservoir strain, 2. LA contractile strain, and 3. LA conduit strain.

Outcome: Incident frailty (dichotomized as frail vs pre-frail/robust) will be ascertained at V6 and V7, based on Fried frailty criteria. Weakness, slowness, exhaustion, weight loss, and low physical activity are the 5 primary components used to define frailty status. Participants were determined to be robust if they have no frailty components present, pre-frail if they have 1 or 2 components, or frail if they have at least 3 of the 5 components. Participants who were frail at either visit 6 or visit 7 will be considered as having incident frailty during follow-up. Participants who were not detected as being frail at visit 6 or visit 7 will be considered as not having incident frailty during follow-up.

Covariates: Age, sex, race-ARIC field center, BMI, diabetes, SBP, antihypertensive medication use, prevalent stroke, prevalent AF, prevalent HF, prevalent dementia, CHD, and left ventricular function evaluated on two-dimensional Doppler echocardiogram.

Data analysis

Baseline characteristics of participants will be described using means and proportions stratified by frail vs. not frail.

For our primary analysis, logistic regression will be used to explore the relationships between LA strain and frailty. The 3 LA strain variables will be analyzed as continuous variables per-standard deviation decrement and as categorical variables in quintiles (highest quintile as reference).

The following models will be used -

Model 1 will adjust for age, sex, and race-ARIC field center.

Model 2 will additionally adjust for baseline cardiovascular characteristics/comorbidities such as BMI, diabetes, SBP, antihypertensive medication use, prevalent stroke, prevalent AF, prevalent HF, prevalent dementia, and CHD.

Model 3 will further adjust for cardiac function evaluated on two-dimensional Doppler echocardiogram such as left atrial volume index, E/e' ratio, and LV longitudinal strain.

We will evaluate interactions by sex and race and perform sex- and race-stratified analyses.

Sensitivity analysis will be performed by excluding participants with prevalent stroke, prevalent AF, prevalent HF, or prevalent dementia. Further, stabilized inverse probability weighting (sIPW) will be used to account for bias due to selective participation in frailty assessments and attrition over follow-up.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __x__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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? ____ 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 current derived consent file ICTDER05 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/aricproposals/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: Wendy Wang … Lin Yee Chen. Association of Left Atrial Function with Neurocognitive Outcomes in the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS)

#3962: Romil R. Parikh … Lin Yee Chen. Association of Atrial Fibrillation with Incident Frailty Among Older Adults in the Community: The Atherosclerosis Risk in Communities (ARIC) Study.

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 https://sites.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.

References

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