ARIC Manuscript Proposal #4226

PC Reviewed: 4/11/23	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of Left Atrial Function with Valvular Heart Disease: The Atherosclerosis Risk in Communities (ARIC) Study.

b. Abbreviated Title (Length 26 characters): LA Function and VHD

2. Writing Group:

Writing group members: Chunxiao Zhang, * Wendy Wang,* Riccardo M. Inciardi, Yuekai Ji, Khaled Shelbaya, Anne Eaton, Alvaro Alonso, Elsayed Z. Soliman, Scott D. Solomon, Amil M. Shah,† Lin Yee Chen† , and others welcome

*,† contribute equally to this paper

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

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3. Timeline: Data collection has been completed. Data analysis and manuscript preparation will be done in the next 6 months.

4. Rationale:

Valvular heart disease (VHD) is highly prevalent in older people in the general population[1-3]. It is associated with multiple adverse events, such as all-cause mortality, incident heart failure (HF), and incident atrial fibrillation (AF)[1,3]. According to recent guidelines, VHD can be classified as four stages (stage A, B, C and D)[4,5]. Early stages of VHD, such as stage A and B, are also associated with adverse cardiovascular (CV) events[1]. Moreover, VHD progresses over time, which worsens prognosis.

Atrial myopathy—characterized by abnormal structure and function of the left atrium (LA)[6]—is associated with adverse CV events, such as HF, AF, and ischemic stroke[7-9]. Recent evidence suggests that lower (poorer) LA function is associated with functional mitral regurgitation (MR)[10-12], a subtype of MR. Moreover, impaired LA function is a strong risk factor for AF, which in turn leads to atrial functional MR[12]. However, whether lower LA function is associated with other VHD, such as aortic regurgitation (AR) or aortic stenosis (AS), is unknown.

Besides echocardiographic-based LA strain, P-wave parameters (PWP) are electrocardiogram (ECG) surrogates of atrial myopathy. The parameters include P wave terminal force in lead V1 (PTFV1), P wave axis, P wave duration, P wave dispersion, and advanced interatrial block[6]. Whether these ECG surrogates of atrial myopathy are associated with VHD is unknown.

Therefore, we aim to evaluate the association of echocardiographic-based LA function and ECG parameters at Visit 5 with prevalence of VHD at Visit 5 and progression of VHD from Visit 5 to Visit 7.

5. Main Hypothesis/Study Questions:

Aim 1: Evaluate association of LA function with VHD.
Hypothesis 1A: Lower LA function will be cross-sectionally associated with higher prevalence of VHD (composite of AR, MR, AS with stage A to D) at Visit 5.
Hypothesis 1B: Lower LA function will be associated with progression of VHD from Visit 5 to Visit 7.

Aim 2: Evaluate association of PWP with VHD.
Hypothesis 2A: Abnormal PWPs will be cross-sectionally associated with higher prevalence of VHD (AR, MR, AS with stage A to D) at Visit 5.
Hypothesis 2B: Abnormal PWPs will be associated with progression of VHD from Visit 5 to Visit 7.

As secondary aims, we will also evaluate association of LA function and PWPs with individual VHD: AR, MR, and AS.

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 1A and 2A: Cross-sectional at Visit 5
Aim 1B and 2B: Prospective cohort study design (Visit 5 to Visit 7).

Inclusion: For Aim 1A and 2A, participants with LA function and ECG data at Visit 5. For Aim 1B and 2B, participants with LA function and ECG data at Visit 5 and with follow-up echo at Visit 7,

Exclusion: History of valve replacement and repair at Visit 5, any stage of mitral stenosis (MS), missing covariates, participants who reported race other than Black or White or non-White participants at the Minneapolis and Forsyth County field centers due to low numbers. For analysis of P wave parameters, we were also exclude participants with AF at visit 5 ECG.

Variables
Exposures:
The following LA function measures (obtained at visit 5) will be assessed continuously (per 1-SD decrement) and categorically as quintiles (highest quintile as referent)
1. LA reservoir strain
2. LA contractile strain
3. LA conduit strain
4. LA volume index.

P wave parameters will be assessed as binary categorical variables using predetermined cut-offs.
1. Abnormal P-wave terminal force in lead V1 (aPTFV1, >= 4000 uV x ms)
2. Abnormal P-wave axis (aPWA >75° or <0°)
3. Prolonged P-wave duration, (PPWD >120 ms)
4. Advanced Interatrial block (a-IAB)

Outcome:
For Aim 1A and 2A: Prevalence of VHD (i.e., Stage A to D) classified on the AHA stage classification at V5.
For Aim 1B and 2B: Progression of VHD: A binary variable defined as worse VHD stage at V7 compared to the VHD stage at V5.

Stage A at risk for valve dysfunction, including AV sclerosis, mitral annular calcification, mitral valve prolapses, and mild MR.
Stage B progressive valvular dysfunction, including mild AS or AS, moderate MR or eccentric jet with mild MR.
Stage C severe asymptomatic valve dysfunction.
Stage D severe symptomatic valve dysfunction.
Stage C and D include severe AS, AR or MR.

MR was quantified as MR jet area / left atrial area ratio.
AS was quantified with trans valvular AV peak jet velocity and AV area at Doppler.
AR was qualitatively assessed by overreading echocardiographers on the basis of color Doppler signal.

Covariates
Age, sex, race, body mass index (BMI), diabetes, coronary heart disease (CHD), HF, AF, ARIC field center, smoking status, systolic blood pressure, antihypertensive medication use, educational level, HF medication, stroke, LA volume index, LV ejection fraction, E/e', LV mass index.

Data analysis
Baseline characteristics will be described as mean ± SD for continuous variables and proportions for categorical variables.

- For Aim 1A and 2A, logistic regression models will be used to estimate the association of LA function and PWP with prevalence of VHD stage at V5.

- For Aim 1B and 2B, logistic regression models will be used to estimate the association of LA function and PWP with the progression of VHD from visit 5 to visit 7.

For all analyses, the following models will be used:
- Model 1 will be adjusted for baseline age, sex, race/center, education level.
- Model 2 will be adjusted for model 1 plus BMI, diabetes, CHD, HF, AF, smoking status, systolic blood pressure, antihypertensive medication use, stroke.
- Model 3 will be adjusted for model 2 plus LA volume index, LV ejection fraction, E/e', LV mass index.

-Sensitivity analysis: we will repeat the analysis above excluding participants with prevalent AF and HF. And inverse probability weighting will be incorporated into the sensitivity analysis to handle the missing data.

-We will test effect modification by sex, age (dichotomized using the median as the cut-off), race. Stratified analyses will be reported when appropriate.

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)?

#2739. Valvular heart disease and cardiac remodeling, damage, and overload in older adults
#3168. Atrial Fibrillation in Patients with Mitral Regurgitation Admitted with Heart Failure in the ARIC Community Surveillance: Prevalence, Correlates, and Impact on Outcomes

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

11.b. If yes, is the proposal

_X_ A. primarily the result of an ancillary study (list number* 2015.29, 2015.34)

___ 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.

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