ARIC Manuscript Proposal #4118

PC Reviewed: 9/13/22	**Status: _____**	**Priority:2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a) Full Title: Association of central and peripheral arterial stiffness with left atrial function

b) Abbreviated Title (Length 26 characters): Arterial stiffness and left atrial strain

2. Writing Group:
Lorraine Mascarenhas, Yuekai Ji, Riccardio Inciardi, Romil Parikh, Anne Eaton, Susan Cheng, Alvaro Alonso, Amil M. Shah, Scott D. Solomon, Michelle L. Meyer, Lin Yee Chen, and others welcome

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline: Statistical analysis: 3 months
Manuscript preparation: 6 months

4. Rationale:

Atrial myopathy—characterized by abnormal left atrial (LA) size and function—is associated with higher risk of atrial fibrillation (AF) and stroke [1,2]. Recent evidence suggests that impaired LA function has prognostic implications in cardiovascular disease. Notably, alterations in left atrial function precede changes in LA size [3,4]. Left atrial strain analysis is useful to assess LA function throughout the cardiac cycle[5]. Strain analysis has utility in predicting cardiovascular events, determining stroke risk in AF patients, and serving as an independent prognostic marker for patients with heart failure[6–8]. Despite its prognostic utility, little is known about risk factors for decreased LA function and strain. Identification of such risk factors may provide new targets for preventative therapies. A potential modifiable risk factor is arterial stiffness, an independent predictor of cardiovascular morbidity and risk factor for incident atrial fibrillation [9–14]. However, its relationship to LA dysfunction remains unclear.

A large cohort study in Japan of 1,156 patients found that increased arterial stiffness, measured through cardio-ankle vascular index (CAVI), was independently associated with lower LA reservoir and conduit strain[15]. Additional studies have demonstrated similar inverse correlations between strain and arterial stiffness [16–20]. However, previous studies have mostly been single-center and included individuals with pre-existing conditions such as type 2 diabetes, hypertension, or atrial fibrillation. Additionally, the studies, on average, had smaller sample sizes typically fewer than two hundred participants.

Therefore, in this study we aim to use data from the Atherosclerosis Risk in Communities data to address the foregoing knowledge gaps. The ARIC study is well-suited to address the limitations of previous studies. It is multi-centered, community-based, and a large sample size of roughly 4,090 participants is appropriate for our investigation.

5. Main Hypothesis/Study Questions:

1) Evaluate the association of central and peripheral arterial stiffness with LA strain

Hypothesis: Higher central arterial stiffness, but not peripheral arterial stiffness, will be associated with lower LA strain

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 – cross sectional at Visit 5

Study population

- Inclusion criteria: ARIC participants at Visit 5 with pulse wave velocity measurements and 2D echocardiographic left atrial strain measurements
- Exclusion criteria: BMI ≥40 kg/m2, evidence of a major arrhythmia on the 12-lead ECG (MN code 8-1-3, 8-3-1, 8-3-2), self-reported aortic revascularization surgery (aorta repaired), aortic aneurysm, flag for MN codes 8-1-2 that influenced PWV waveforms, aortic stenosis, moderate or severe aortic regurgitation, prevalent heart failure, prevalent coronary artery disease, missing covariates, participants who reported race other than Black or White or non-White participants at the Minneapolis and Washington County field centers due to low numbers.

Exposures: Arterial Hemodynamics

Our independent variables will be individual measures of pulse wave velocity (PWV), which was obtained using a non-invasive and automated waveform analyzer (VP1000 plus; Omron Co., Komaki, Japan) at visit 5 (2011-2013). PWV was calculated as the distance (centimeters) the pressure waveforms traveled between the heart and arterial sites of interest over time (seconds). The average of 2 PWV measurements was recorded for each participant. Central (carotid-femoral PWV, heart-femoral PWV, heart-carotid PWV) and peripheral (femoral-ankle PWV) measures of stiffness were obtained. For this study, our main exposures will be carotid-femoral PWV (cfPWV) and femoral-ankle PWV (faPWV), which will be assessed continuously and as categories (e.g., quartiles), as appropriate. Values at the 1st and 99th percentile of the distribution will be winsorized.

Outcomes: LA strain

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

1. LA reservoir strain
2. LA contractile strain
3. LA conduit strain

Covariates

Covariates were obtained at visit 5 and the following variables will be considered for inclusion in our models: age, sex, race-center, BMI, mean arterial pressure, estimated glomerular filtration rate (eGFR), tobacco use, alcohol use, diabetes, and hyperlipidemia.

Statistical analysis

Participants' baseline characteristics will be compared across quartiles of each PWV measure using means (± standard deviation [SD]) for normally distributed data, median (interquartile interval [IQI]) for non-normally distributed data, and frequency (percentage) for binary/categorical data.

We will use multivariable linear regression to assess the association of cfPWV and faPWV (as continuous variables and as quartiles) with LA function measures. Models will be adjusted as follows

- Model 1 will adjust for age, sex, race-center
- Model 2 will be adjusted for mean arterial blood pressure, BMI, eGFR, type 2 diabetes, HDL, LDL, triglycerides, tobacco use, alcohol use, antihypertensive medication use
- Model 3 will adjust for left ventricular (LV) mass index, LV longitudinal strain, and E/e' average

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? ____ 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)?

The most relevant manuscripts include:
#3396: Arterial stiffness and AF risk- Alvaro Alonso
#2694: CAVI in older adults- Kunihiro Matsushita
#2048: Association of myocardial deformational measures and arterial stiffness in the community- Susan Cheng

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

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)*)

2015.29
2015.23

*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.

References:

1. Rivner H, Mitrani RD, Goldberger JJ. Atrial Myopathy Underlying Atrial Fibrillation. *Arrhythm Electrophysiol Rev*. 2020;9(2):61-70. doi:10.15420/aer.2020.13
2. Shen MJ, Arora R, Jalife J. Atrial Myopathy. *JACC Basic Transl Sci*. 2019;4(5):640-654. doi:10.1016/j.jacbts.2019.05.005
3. Hoit BD. Left atrial size and function: role in prognosis. *J Am Coll Cardiol*. 2014;63(6):493-505. doi:10.1016/j.jacc.2013.10.055

4. Chen C, Yang Y, Ma W, Qi L, Zhang B, Zhang Y. Left atrial phasic function remodeling during its enlargement: a two-dimensional speckle-tracking echocardiography study. *BMC Cardiovasc Disord*. 2022;22(1):231. doi:10.1186/s12872-022-02672-z
5. Gan GCH, Ferkh A, Boyd A, Thomas L. Left atrial function: evaluation by strain analysis. *Cardiovasc Diagn Ther*. 2018;8(1):29-46. doi:10.21037/cdt.2017.06.08
6. Hoit BD. Assessment of Left Atrial Function by Echocardiography: Novel Insights. *Curr Cardiol Rep*. 2018;20(10):96. doi:10.1007/s11886-018-1044-1
7. Malagoli A, Rossi L, Bursi F, et al. Left Atrial Function Predicts Cardiovascular Events in Patients With Chronic Heart Failure With Reduced Ejection Fraction. *J Am Soc Echocardiogr*. 2019;32(2):248-256. doi:10.1016/j.echo.2018.08.012
8. Hsu PC, Lee WH, Chu CY, et al. Prognostic role of left atrial strain and its combination index with transmitral E-wave velocity in patients with atrial fibrillation. *Sci Rep*. 2016;6:17318. doi:10.1038/srep17318
9. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;55(13):1318-1327. doi:10.1016/j.jacc.2009.10.061
10. Laurent S, Boutouyrie P, Asmar R, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension*. 2001;37(5):1236-1241. doi:10.1161/01.hyp.37.5.1236
11. Sarafidis PA, Loutradis C, Karpetas A, et al. Ambulatory Pulse Wave Velocity Is a Stronger Predictor of Cardiovascular Events and All-Cause Mortality Than Office and Ambulatory Blood Pressure in Hemodialysis Patients. *Hypertension*. 2017;70(1):148-157. doi:10.1161/HYPERTENSIONAHA.117.09023
12. Georgianos PI, Sarafidis PA, Lasaridis AN. Arterial stiffness: a novel cardiovascular risk factor in kidney disease patients. *Curr Vasc Pharmacol*. 2015;13(2):229-238. doi:10.2174/15701611113119990147
13. Shchetynska-Marinova T, Liebe V, Papavassiliu T, et al. Determinants of arterial stiffness in patients with atrial fibrillation. *Arch Cardiovasc Dis*. 114(8-9):550-560. doi:10.1016/j.acvd.2020.12.009
14. Almuwaqqat Z, Claxton J 'Neka S, Norby FL, et al. Association of arterial stiffness with incident atrial fibrillation: a cohort study. *BMC Cardiovasc Disord*. 2021;21(1):247. doi:10.1186/s12872-021-02057-8
15. Yoshida Y, Nakanishi K, Daimon M, et al. Association of arterial stiffness with left atrial structure and phasic function: a community-based cohort study. *J Hypertens*. 2020;38(6):1140-1148. doi:10.1097/HJH.0000000000002367
16. Nemes A, Piros G, Domsik P, et al. Correlations between three-dimensional speckle-tracking echocardiography-derived left atrial functional parameters and aortic stiffness in healthy subjects - Results from the MAGYAR-Healthy Study. *Acta Physiol Hung*. 2015;102(2):197-205. doi:10.1556/036.102.2015.2.10
17. van Schinkel LD, Auger D, van Elderen SGC, et al. Aortic stiffness is related to left ventricular diastolic function in patients with diabetes mellitus type 1: assessment with MRI and speckle tracking strain analysis. *Int J Cardiovasc Imaging*. 2013;29(3):633-641. doi:10.1007/s10554-012-0125-2
18. Oishi Y, Miyoshi H, Iuchi A, Nagase N, Ara N, Oki T. Negative impact of cardiovascular risk factors on left atrial and left ventricular function related to aortic stiffness--new application of 2-dimensional speckle-tracking echocardiography. *Circ J*. 2013;77(6):1490-1498. doi:10.1253/circj.cj-12-1260
19. Tabata T, Shimizu K, Morinaga Y, et al. The Relationship Between Cardio-Ankle Vascular Index and Left Atrial Phasic Function in Hypertensive Patients With Preserved Ejection Fraction. *Front Med Technol*. 2021;3:724089. doi:10.3389/fmedt.2021.724089
20. Kilicgedik A, Ç Efe S, Gürbüz AS, et al. Left Atrial Mechanical Function and Aortic Stiffness in Middle-aged Patients with the First Episode of Atrial Fibrillation. *Chin Med J (Engl)*. 2017;130(2):143-148. doi:10.4103/0366-6999.197979