ARIC Manuscript Proposal #3599

PC Reviewed: 4/14/20 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Association of Leisure Time Physical Activity with Left Atrial Function in Older Age: the ARIC Study

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

2. Writing Group:

Writing group members: Romil Parikh, Riccardo Inciardi, Wendy Wang, Sheila H. Hegde, Faye L. Norby, Michael Zhang, Jorge Reyes Castro, Alvaro Alonso, Amil M. Shah, Scott D. Solomon, Lin Yee Chen

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

First author: Romil Parikh
Address: Division of Epidemiology & Community Health, 300 West Bank Office Building, 1300 S. 2nd St., Minneapolis, MN 55454
Phone: 6128405816 Fax:
E-mail: parik075@umn.edu

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).

Name: Lin Yee Chen MD MS
Address: Cardiac Arrhythmia Center, Cardiovascular Division,
Department of Medicine, University of Minnesota Medical School,
420 Delaware Street SE, MMC 508, Minneapolis, MN 55455.

Phone: +1 612-625-4401 Fax: +1 612-624-4937
E-mail: chenx484@umn.edu

3. Timeline:

Analyses in 4 months and first draft of manuscript in 4 months.

4. Rationale:

Recent evidence indicates that impaired left atrial (LA) function is associated with increased risk of ischemic stroke, heart failure, and cardiovascular death.[1-6] Notably, these associations are independent of atrial fibrillation (AF) and LA enlargement.[7, 8] Despite the important prognostic

role of impaired LA function, very little is known regarding its pathogenesis, particularly as relates to modifiable lifestyle risk factors.

Physical activity (PA) is a cost-effective and modifiable lifestyle factor that may have salutary effects on cardiac remodeling.[9-11] For substantial health benefits, the 2018 Physical Activity Guidelines (PAG) recommends that adults engage in at least 150 minutes of moderate intensity physical activity or 75 minutes of vigorous intensity physical activity, or an equivalent combination of both moderate and vigorous intensity physical activity (MVPA) per week.[10] In the ARIC cohort, a previous study reported that PAG recommended ideal leisure time physical activity (LTPA), higher average levels of LTPA over a 24-year period, and an improvement in LTPA even later in life were associated with more favorable indices of left ventricular (LV) diastolic and systolic function in older adults.[11] However, there was no significant association between LTPA and LA size as measured by LA volume index (LAVi).[11]

In the present study, we aim to extend this line of investigation by evaluating the association of LTPA with **LA function** in older age.

5. Main Hypothesis/Study Questions:

Aim: To evaluate the association of LTPA with LA function at Visit 5
H_1: Higher LTPA at Visit 5 will be associated with higher LA contractile, conduit and reservoir functions at Visit 5.
H_2: Higher levels of LTPA over Visits 1, 3, and 5 will be associated with higher LA contractile, conduit and reservoir functions at Visit 5.
H_3: Between Visits 3 and 5, compared to persistently poor LTPA, persistently higher LTPA and increasing LTPA will be associated with higher LA contractile, conduit and reservoir functions at Visit 5.

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: For H_1, we will conduct a cross-sectional analysis of LTPA and LA function measured at Visit 5. For H_2, we will evaluate the association of LTPA over Visits 1, 3, 5 (a continuous cumulative average and a categorical variable) with LA function at Visit 5. For H_3, we will evaluate the association of change in LTPA between Visit 3 and 5 with LA function at Visit 5.

Inclusion/Exclusion criteria: We will include all participants with LA function data at Visit 5 and exclude those with missing LTPA and covariate data at Visit 5, and those with prevalent AF and HF at Visit 5. For H_2 and H_3, we will also exclude those with missing LTPA data at Visits 1 and 3.

Exposure: LTPA data were collected at Visits 1, 3 and 5 with the sports and exercise component of the Baecke questionnaire. LTPA data will be quantified as average MET-min/week as described in previously published work. LTPA will then be examined continuously and categorically based on intensity of activity (as previously described)[11]: i) Ideal/recommended ii) Intermediate iii) Poor.

Outcomes: 2D echocardiographic LA function variables measured at Visit 5: LA reservoir, conduit and contractile function (all variables will be assessed continuously).

Covariates of interest: (measured at visit 5)

- Demographic variables: age, sex, race-field center and body mass index (BMI)
- Cardiovascular risk factors: systolic (SBP) and diastolic (DBP) blood pressure, hypertension medications, diabetes (DM), smoking status (current, former, never)
- Clinical conditions: coronary heart disease (CHD), stroke.
- Echocardiographic variables: left atrial volume index (LAVi), left ventricular longitudinal strain (LVLS), E/e'

Statistical analysis:

- Participant characteristics will be described using mean ± standard deviation for continuous variables, median (interquartile range) for highly skewed variables, and proportions for categorical variables, stratified by LTPA categories.
- For H_1, linear regression will be used to evaluate the relationship between LTPA and LA function. LA function variables will be presented as adjusted means ± standard error. We will fit the following multivariable regression models:
    - Model 1: Adjusted for age, sex, race/field center,
    - Model 2: Model 1 + SBP, DBP, hypertension medications, DM, CHD, stroke, BMI, smoking
    - Model 3: Model 2 + LAVi, LVLS, E/e'

- For H_2, total cumulative average LTPA will be calculated accounting for the time intervals between Visits 1, 3, and 5 for each participant. Average LTPA during the interval between visits will be calculated by averaging the activity obtained at the beginning and end of each interval. Missing LTPA estimates at visits 1 or 3 will be imputed using the average of available values from neighboring visits. Associations between total cumulative average LTPA and measures of LA function will be evaluated using restricted cubic spline models and linear regression models:
    - Model 1: Adjusted for age, sex, race/field center,
    - Model 2: Model 1 + SBP, DBP, hypertension medications, DM, CHD, stroke, BMI, smoking
    - Model 3: Model 2 + LAVi, LVLS, E/e'

- For H_3, change in LTPA between Visits 3 and 5 will be assessed categorically as groups of participants with poor LTPA, decreased LTPA, increased LTPA, and persistently high LTPA. Measures of LA function will be compared between groups, relative to the persistently poor LTPA group, by multivariable linear regression:
    - Model 1: Adjusted for age, sex, race/field center,
    - Model 2: Model 1 + SBP, DBP, hypertension medications, DM, CHD, stroke, BMI, smoking
    - Model 3: Model 2 + LAVi, LVLS, E/e'

Limitations:

LTPA is self-reported, and is subject to recall bias; however, Baecke's questionnaire and derived measures of LTPA have been previously validated. Over-reporting of LTPA is plausible and may bias the results towards the null. Despite adjusting for potential confounders, there may be residual confounding.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes _xx___ 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 __xx_ 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"? __xx__ 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

___xx___ 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)?

MS #2411: Physical Activity and Cardiac Structure and Function in an Elderly Cohort [This MS evaluated LA size as indicated by LAVi, we propose to evaluate LA function.]

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _xx___ Yes ____ No

11.b. If yes, is the proposal

_xx__ A. primarily the result of an ancillary study (list number* ___2015.29 (Chen)

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

References:

1. Gonçalves A, Hung CL, Claggett B, et al. Left Atrial Structure and Function Across the Spectrum of Cardiovascular Risk in the Elderly: The Atherosclerosis Risk in Communities Study. Circ Cardiovasc Imaging. 2016;9(2):e004010.
2. Gupta DK, Shah AM, Giugliano RP, et al. Left atrial structure and function in atrial fibrillation: ENGAGE AF-TIMI 48. Eur Heart J. 2014;35(22):1457–1465.
3. Santos AB, Kraigher-Krainer E, Gupta DK, et al. Impaired left atrial function in heart failure with preserved ejection fraction. Eur J Heart Fail. 2014;16(10):1096–1103.
4. Hoit BD. Left atrial size and function: role in prognosis. Journal of the American College of Cardiology. 2014;63:493–505. doi: 10.1016/j.jacc.2013.10.055.
5. Gan GCH, Ferkh A, Boyd A, Thomas L. Left atrial function: evaluation by strain analysis. Cardiovasc Diagn Ther. 2018;8(1):29–46.
6. Parameswaran R, Kalman JM. Left Atrium and Cardiovascular Risk: Does Functionality Matter More Than Size? J Am Heart Assoc. 2018;7(7):e008930. Published 2018 Mar 30. doi:10.1161/JAHA.118.008930
7. Sardana M, Nah G, Tsao CW, et al. Clinical and Echocardiographic Correlates of Left Atrial Function Index: The Framingham Offspring Study. J Am Soc Echocardiogr. 2017;30(9):904–912.e2. doi:10.1016/j.echo.2017.05.013
8. Wong JM, Welles CC, Azarbal F, Whooley MA, Schiller NB, Turakhia MP. Relation of left atrial dysfunction to ischemic stroke in patients with coronary heart disease (from the Heart and Soul Study). Am J Cardiol 2014;113:1679–84.
9. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation 2019; 139: e56-528. doi: 10.1161/CIR.0000000000000659
10. U.S. Department of Health and Human Services. Physical Activity Guidelines for Americans, 2nd edition. Washington, DC: U.S. Department of Health and Human Services; 2018.
11. Hegde SM, Gonçalves A, Claggett B, et al. Cardiac structure and function and leisure-time physical activity in the elderly: The Atherosclerosis Risk in Communities Study. Eur Heart J. 2016;37(32):2544–2551. doi:10.1093/eurheartj/ehw121