ARIC Manuscript Proposal #2411

PC Reviewed: 8/12/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Physical Activity and Cardiac Structure and Function in an Elderly Cohort

b. Abbreviated Title (Length 26 characters): Physical Activity and Echo

2. Writing Group:

Writing group members: Sheila Hegde, Alexandra Gonçalves, Brian Claggett, Amil Shah, Kelly Evenson, Aaron Folsom, Scott D. Solomon, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __SH__ **[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: Analysis will begin following proposal approval with anticipated manuscript completion within 6 months.

4. Rationale:

Physical activity is known to have an inverse relationship with adverse cardiovascular (CV) outcomes.[1, 2] Leisure-time physical activity, even in small doses, has been demonstrated to be protective of CV events, including in the aging ARIC population.[2-4] The mechanism of the risk reduction in adverse cardiovascular outcomes associated with physical activity is likely multifactorial. One possible explanation is that physical inactivity may be associated with the presence of subclinical abnormalities in cardiac structure and function, particularly myocardial deformation and diastolic function.

The aging heart is characterized by an increasing prevalence of heart failure with preserved ejection fraction (HFpEF), which accounts for substantial mortality, ranging from 10-30% annually.[5] Longitudinal data from the Framingham population demonstrate that the cardiac remodeling associated with aging is further characterized by increasing LV wall thickness, decreasing LV dimensions, and increasing fractional shortening. [6] Exercise training in the elderly has been associated with improvements in functional capacity, peak myocardial oxygen consumption, and quality of life, however a clear improvement in diastolic dysfunction has not been demonstrated.[7-9] Animal studies further suggest that the mechanisms mediating the protective effects of chronic exercise in pressure-overload models are associated with a decrease in myocardial fibrosis, promotion of compliant extracellular matrix components, inhibition of mitochondrial dysfunction, and preservation of myocardial oxygen balance.[10, 11] The effects of these various metabolic changes may be characterized by clinical and subclinical changes in cardiac structure and function. The relationships between self-reported measures of physical activity and cardiac structure and function, particularly myocardial deformation, have not been previously described in a large elderly population.

5. Main Hypothesis/Study Questions:

Primary hypothesis:

1) Poor physical activity at Visit 5 will be associated with abnormal measures of cardiac structure and function.

Secondary hypotheses:

1) Low levels of physical activity over Visits 1, 3, and 5 will be associated with abnormal measures of cardiac structure and function.

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 and Inclusion/Exclusion Criteria:

This study will be a secondary analysis of a prospective cohort study. The primary analysis will be a cross-sectional analysis of physical activity data and echocardiography parameters obtained during Visit 5. Secondary analysis will involve an evaluation of physical activity over Visits 1, 3, 5 as both a continuous cumulative average and a

categorical variable and its respective association with echocardiography parameters from Visit 5.

The study sample will include all patients who underwent echocardiography during Visit 5 (2011-2013) with images of acceptable quality for analysis.

For the initial cross-sectional analysis, those with prevalent cardiovascular disease (CHD, stroke, HF, severe valvular disease) and with missing physical activity data at Visit 5 will be excluded. For the secondary analysis, participants will be excluded if physical activity data is missing at Visits 1, 3, or 5.

Exposures variables:

1. Physical activity
    a. Measurement
        i. Assessed by previously validated modified Baecke Physical Activity questionnaire
        ii. Composite score
            1. For each category of activity: leisure, sports, work index
        iii. Stratification
            1. Intensity of activity (as previously described)[1]
                a. Recommended
                b. Intermediate
                c. Poor
    b. Analysis
        i. Cross sectional analysis at Visit 5
        ii. Cumulative average[1] of activity over Visits 1, 3, 5
        iii. Categorize participants into groups based on activity intensity over the 3 visits

Outcome variables:

The primary and secondary outcome variables of interest include the following Visit 5 echo-derived parameters of cardiac structure and function:

1. LV dimensions, volumes, ejection fraction
2. LV diastolic function-related measures
3. LA dimensions
4. LV global, longitudinal, radial, and circumferential strain
5. RV dimensions, volumes, ejection fraction

Covariates of interest: (Visit 5)

1. Demographics: Age, Gender, Race/ethnicity, Field site, Education, Socioeconomic status, Obesity (BMI > 30)
2. Cardiovascular risk factors: Hypertension (SBP≥140 mmHg, DBP≥ 90 mmHg), Diabetes (A1C), Smoking status (current, former, never), Dyslipidemia
3. Clinical characteristics: COPD and asthma, Alcohol intake, Diet
4. Lab values: BNP, troponin

Analysis plan:
Descriptive statistics of the overall population will be presented as well as stratification by physical activity category. Continuous normally distributed data will be displayed as mean and standard deviation values. Continuous non-normally distributed data will be displayed as median and interquartile range values. Categorical data will be reported as percent frequencies and compared by chi-squared or Fischer exact tests. Continuous data will be compared by Wilcoxon rank sum tests or t tests as appropriate. Single variable and multivariable linear regression analysis will be performed to evaluate the cross-sectional relationships between physical activity and various echocardiographic parameters. For significant correlates, we will test for effect modification by age, gender, and race, acknowledging the potential for false positives due to multiple testing. A two-sided p-value of < 0.05 will be considered statistically significant.

Limitations:
A limitation of the cross-sectional design will be the inability to make conclusions about causality. Use of the modified Baecke questionnaire is a self-reported variable, which may result in recall bias; however, this questionnaire has been previously validated. Additionally, in evaluating Visit 5 patients, there is a survival bias as they may represent a healthier population.

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)?

Physical Activity and Echocardiographic Characteristics in an African American Cohort #634
Physical Activity Patterns and Predictors of Change in ARIC #333
Physical activity and incidence of cardiovascular disease in African Americans #1715

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

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)
___ 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 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. Bell EJ, Lutsey PL, Windham BG, Folsom AR. Physical activity and cardiovascular disease in African Americans in Atherosclerosis Risk in Communities. *Med Sci Sports Exerc*. 2013; 45(5):901-7.
2. Lee DC, Pate RR, Lavie CJ, Sui X, Church TS, Blair SN. Leisure-time running reduces all-cause and cardiovascular mortality risk. *J Am Coll Cardiol.* 2014 Aug 5;64(5):472-81.
3. Wen CP, Wai JP, Tsai MK, Chen CH. Minimal amount of exercise to prolong life: to walk, to run, or just mix it up? *J Am Coll Cardiol.* 2014 Aug 5;64(5):482-4
4. Wen CP, Wai JP, Tsai MK, Yang YC, Cheng TY, Lee MC, Chan HT, Tsao CK, Tsai SP, Wu X. Minimum amount of physical activity for reduced mortality and

extended life expectancy: a prospective cohort study. *Lancet.* 2011 Oct 1;378 (9798):1244-53.
5. Chan MM, Lam CS. How do patients with heart failure with preserved ejection fraction die? *Eur J Heart Fail.* 2013 Jun;15(6):604-13.
6. Cheng S1, Xanthakis V, Sullivan LM, Lieb W, Massaro J, Aragam J, Benjamin EJ, Vasan RS. Correlates of echocardiographic indices of cardiac remodeling over the adult life course: longitudinal observations from the Framingham Heart Study. *Circulation.* 2010 Aug 10;122(6):570-8.
7. Barmeyer A1, Müllerleile K, Mortensen K, Meinertz T. Diastolic dysfunction in exercise and its role for exercise capacity. *Heart Fail Rev*. 2009 Jun;14(2):125-34.
8. Smart N1, Haluska B, Jeffriess L, Marwick TH. Exercise training in systolic and diastolic dysfunction: effects on cardiac function, functional capacity, and quality of life. *Am Heart J.* 2007 Apr;153(4):530-6.
9. Kappagoda T1, Amsterdam EA. Exercise and heart failure in the elderly. *Heart Fail Rev*. 2012 Sep;17(4-5):635-62.
10. Marshall KD, Muller BN, Krenz M, Hanft LM, McDonald KS, Dellsperger KC, Emter CA. Heart failure with preserved ejection fraction: chronic low-intensity interval exercise training preserves myocardial O2 balance and diastolic function. *J Appl Physiol* (1985). 2013 Jan 1;114(1):131-47.
11. Emter CA1, Baines CP. Low-intensity aerobic interval training attenuates pathological left ventricular remodeling and mitochondrial dysfunction in aortic-banded miniature swine. *Am J Physiol Heart Circ Physiol.* 2010 Nov;299(5):H1348-56.