ARIC Manuscript Proposal #3595

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

1. **a. Full Title** Longitudinal changes in pulmonary pressure in late life: the ARIC study

   b. Abbreviated Title (Length: 26 characters): Change in pulmonary pressure

2. **Writing Group:**
   Writing group members: Rani Zierath, Brian Claggett, Hicham Skali, Kunihiro Matsushita, Dalane Kitzman, Suma Konety, Thomas Mosley, Amil Shah; others welcome

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

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3. **Timeline:**
We will begin analysis once the proposal is approved and anticipate manuscript completion in approximately 6 months following proposal approval.

4. **Rationale:**

Echocardiographic assessment of pulmonary hemodynamics through estimation of the pulmonary artery systolic pressure (PASP) using peak tricuspid regurgitation (TR) velocity is well-established for the diagnosis and management of various cardiovascular and pulmonary conditions [1,2]. Echocardiographically determined PASP is an independent predictor of mortality and heart failure (HF) hospitalization among patients with prevalent HF [2,13,16] with both preserved and reduced ejection fraction[12,13,15,22]. The association of PASP with all-cause and cardiovascular (CV) death in HF is independent of age, sex, LVEF and diastolic function.[12-14] Higher PASP is similarly associated with adverse outcomes in other chronic cardiovascular and non-cardiovascular conditions, including coronary artery disease, HIV infection, and chronic

kidney disease [9-11]. In general population studies, higher PASP is predictive of both mortality and incident HF[3-13]. Cross-sectional analyses in the general population studies have demonstrated that higher PASP is associated with older age, higher BMI, greater pulse pressure, larger left atrial volume, higher E/e' ratio,[3-7] and with right ventricular (RV) dysfunction[2,14,15,17-18].

While the prognostic implications of higher PASP are well established, few data exist regarding longitudinal change in pulmonary pressure in the community. Similarly, little is known about the clinical and imaging predictors of longitudinal changes in PASP in late life. This analysis aims to characterize the longitudinal changes in PASP over ~5 years in late life, and to define the predictors of this change. We will leverage longitudinal echocardiographic data from Visits 5 and 7 of the Atherosclerosis Risk in Communities (ARIC) study. Together with the detailed longitudinal clinical phenotyping, ARIC is a unique resource to address this important gap in knowledge.

5. **Main Hypothesis/Study Questions:**
   We hypothesize that pulmonary pressure increases over time in late life, and that longitudinal increase in pulmonary pressure will be the greatest among persons with cardiovascular comorbidities and/or evidence of left ventricular remodeling or dysfunction at Visit 5.

   Specifically, we aim to:
   1. Define reference limits for the change in pulmonary pressure over time using data from a low-risk cohort free of cardiovascular risk factors, disease, or significant echo abnormalities in both visits 5 and 7.
   2. Describe the changes in pulmonary pressure, measured echocardiographically using the peak tricuspid regurgitation velocity (TR), in an elderly cohort over a ~5-year period.
   3. Determine the clinical and echocardiographic predictors of longitudinal change in pulmonary pressure over a ~5-year period.

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:
   This is a longitudinal analysis using data from both Visit 5 and Visit 7, including clinical, echocardiographic, and laboratory data.

   Inclusion/Exclusion criteria:
   We will include ARIC participants who underwent echocardiography at both Visits 5 and 7. We will exclude participants who did not have assessable TR velocity either Visit. We will also exclude participants with moderate or greater mitral or aortic valve disease at either Visit.

Key variables of interest:

1. Clinical covariates (Visits 5 and 7): age, gender, race/ethnicity, height, weight, blood pressure, heart rate, history of hypertension, diabetes, dyslipidemia, coronary artery disease, prior MI or revascularization procedure, atrial fibrillation, prior stroke or TIA, heart failure, eGFR, serum creatinine, hemoglobin, hematocrit, hemoglobin A1C, fasting glucose.
2. Echocardiographic variables (Visits 5 and 7): (1) LV structure (LV end-diastolic and end-systolic volumes and dimensions), wall thickness, relative wall thickness, and mass); (2) LV diastolic function (E wave, A wave, TDI E', E/e' ratio, LAVi, and LA diameter); (3) LV systolic function (LVEF, global longitudinal strain, global circumferential strain); (4) pulmonary hemodynamics (estimated PASP based on TR jet velocity) and right ventricular function (RV fractional area change, TDI tricuspid annular s').
3. Cardiac biomarkers (Visit 5): NT-proBNP, hs-cTnT.

Data Analysis:

PASP will be defined using the Bernoulli equation and assuming a right atrial pressure of 5 mmHg as follows: $PASP = [4*(TR)^2] + 5$.

Aim 1: Among a previously defined low-risk sub-group of ARIC participants free of echocardiographic abnormalities, cardiovascular disease, and cardiovascular risk factors at Visit 5[20,21], we will use quantile regression (STATA qreg) to determine the 10^{th}, 50^{th}, and 90^{th} percentile limits of PASP change. Limits will be defined in the low risk reference group overall and stratified by sex. The resulting limit will be used as a reference for the overall sample in analysis for Aims 2 and 3 below.

Aim 2: We will describe the distribution of change in PASP from Visits 5 to 7 among the study sample overall. We will further describe the prevalence of 'abnormal' changes in diastolic measures defined using the 90^{th} percentile limit of change defined in Aim 1 above. Values will also be defined in subgroups based on sex, race, and age categories. We will perform additional analyses stratifying based on HF status at Visits 5 and 7.

Aim 3: We will define clinical and imaging predictors of PASP from Visit 5 to 7. Key clinical predictors assessed at Visit 5 will include: age, gender, race/ethnicity, chronic kidney disease, history of atrial fibrillation, history of coronary artery disease including myocardial infarction, hypertension, diabetes, BMI, and smoking status. Key imaging predictors at Visit 5 will include LVEF, LV mass index, LV longitudinal and circumferential strain, LV diastolic indices (e', E/e', LA size), and V5 PASP value. Key model covariates will include the following variables from both Visits 5 and 7: systolic BP, diastolic BP, heart rate, and rhythm during echo (sinus versus atrial fibrillation). Additional models will further adjust for interval myocardial infarction between Visits 5 and 7. For predictors of change in PASP as a continuous variable, we will employ

multivariable linear regression. For predictors of abnormal increase in PASP as a dichotomous variable, we will employ multivariable logistic regression. Additional analyses will be performed stratified by ACCF/AHA Heart Failure Stage at Visit 5 as previously defined[20,21]. Sensitivity analysis will be performed limited to participants free of HF at Visits 5 and 7.

Analyses will be performed with STATA 14.

Anticipated methodologic limitations

- There is variability in the collection of echocardiographic measurements between Visits 5 and 7 due to different sonographers and sites. This will add measurement variability that may reduce the precision of our estimates and power of our analyses. We will report data on intra- and inter-reader variability for PASP, and short-term total variability based on the ARIC Visit 5 repeatability study.
- As the detectability of TR is variable, only a subset of participants will have TR detectable at both Visits. This may limit our power to detect associations of clinical and imaging predictors with change in PASP. Furthermore, to the extent that inability to assess TR is not at random, this may introduce ascertainment. Attendance bias may further impact the generalizability of our findings. We will attempt to mitigate the impact of these biases by performing sensitivity analyses incorporating inverse probability weighting. Probability weights will be based on clinical, echocardiographic, and biomarker values at Visit 5. Death between Visits 5 and 7 will introduce survival bias, which we expect to bias us toward underestimating longitudinal changes in PASP and the associations of predictors with this change.
- The number of participants in our low risk reference group may be limited, particularly due to possible non-assessable TR velocity. This will likely preclude defining race-specific reference limits and may limit the precision of our reference limits for change in PASP. We will employ quantile regression to try to mitigate this limitation.
- Assessment of right atrial pressure is optimally performed based on assessment of inferior vena cava size and collapsibility. However, as these assessments are not available at Visit 5, we will assume a right atrial pressure of 5 mmHg (as commonly done in the literature[3,5,14,15]) for our primary analysis.
- The gold standard for measuring pulmonary hemodynamics, including PASP, is right heart catheterization. The use of echocardiography to estimate PASP, and its longitudinal change, may therefore introduce misclassification. However, echocardiographic estimates have been previously validated[23] and are routinely used clinically.

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

8. **a. Will the DNA data be used in this manuscript? ____ Yes __x__ No**

   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)?**

    ARIC Manuscript Proposal #3314 Impact of left ventricular diastolic function on association between systemic arterial stiffening and elevated pulmonary pressure

    ARIC Manuscript Proposal # 1158 Prevalence and correlates of mitral, tricuspid, and aortic regurgitation in middle-aged and elderly African-Americans: the ARIC study

    ARIC Manuscript Proposal #0452 The longitudinal relationship between diastolic and isolated systolic hypertension

    ARIC Manuscript Proposal #U0141 Right Ventricular Function, Right Ventricular-Pulmonary Artery Coupling, and Heart Failure Risk in 4 US Communities: The Atherosclerosis Risk in Communities (ARIC) Study

    ARIC Manuscript Proposal #0633 Pulmonary function and left ventricular mass in African Americans: 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? ____ Yes __x__ No**

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/

12. **a. 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.**

    b. 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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