ARIC Manuscript Proposal #3600

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

1.a. Full Title: Association of Echocardiographic Measures of Pulmonary Hemodynamics and Right Ventricular Function with Atrial Arrhythmias

b. Abbreviated Title (Length 30 characters) : Pulmonary Hemodynamics and SVT

2. Writing Group: Romil Parikh, Faye Norby, Wendy Wang, Thenappan Thenappan, Kurt Prins, Pamela L. Lutsey, Scott D. Solomon, Amil M. Shah, Lin Y. Chen

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

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3. Timeline:

Statistical analysis: 4 months; Manuscript preparation: 4 months

4. Rationale:

Higher incidence of atrial fibrillation (AF) and atrial flutter in pulmonary hypertension (PH) is associated with poor quality of life, clinical decompensation, and hospitalizations.[1] A postulated mechanism for higher incidence of atrial arrhythmias in PH is that elevated pulmonary vascular pressures is transmitted to the right atrium (RA) through the right ventricle (RV), leading to increased atrial stretch, fibrosis and remodeling. Among patients with heart failure (HF) and preserved ejection fraction, prevalent AF is associated with worse RV function.[2] Additionally, increased sympathetic tone associated with PH and chronic hypoxia may also contribute to the initiation and perpetuation of AF.[1-4]

Previous community-based studies have linked higher pulmonary artery systolic pressure (PASP), regardless of PH, with increased risk of heart failure (HF) and all-cause mortality.[5-7] In the ARIC study, it was reported that lower RV ejection fraction to PASP ratio (worse RV-pulmonary artery or PA coupling) was associated with a higher risk of HF which persisted even after further adjustment for left atrial volume index (LAVi).[8] However, community-based studies on associations of pulmonary hemodynamics with atrial arrhythmias are lacking. In this study, we aim to evaluate the association of pulmonary hemodynamics and RV function with incidence of AF, and frequency of premature atrial contractions (PACs) and paroxysmal supraventricular tachycardias (SVTs).

The findings of our study may underscore the importance of RA and RV remodeling (as opposed to the current paradigm of AF being predominantly due to LA remodeling) in pathogenesis of AF.

5. Main Hypothesis/Study Questions:

Aim: Evaluate the association of pulmonary hemodynamics and RV function measured by echocardiography at Visit 5, with incident AF through 2018, and frequency of PACs and SVTs measured over 2 weeks by Zio XT ®Patch at Visit 6.

H_1: Higher PASP, higher pulmonary vascular resistance (PVR), lower RV function, and lower RV-PA coupling are associated with increased risk of AF.

H_2: Higher PASP, higher PVR, lower RV function, and lower RV-PA coupling are associated with higher frequency of PAC.

H_3: Higher PASP, higher PVR, lower RV function, and lower RV-PA coupling are associated with higher frequency of SVT.

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 evaluate the prospective association of pulmonary hemodynamics and RV function measured by echocardiography at Visit 5 with incident AF through 2018.

- For H_2 and H_3, we will evaluate the prospective association of pulmonary hemodynamics and RV function measured by echocardiography at Visit 5 with frequency of PACs and SVTs measured over 2 weeks by Zio XT ®Patch at Visit 6.

Study population

- We will include all ARIC participants who attended visit 5. We will exclude those with prevalent AF, missing echocardiographic data of interest, covariates of interest, participants of a racial group other than white or black, blacks in Minnesota and Maryland (due to small numbers), and those with valvular heart disease.

- Additionally, for H_2 and H_3, we will further exclude participants with missing Zio XT ®Patch data at Visit 6, for outcome variables of interest.

Exposure measurement

Pulmonary hemodynamics and RV function measured at Visit 5 (as described in previously published work[8]) by:

- 2D echocardiography:

1) Pulmonary artery systolic pressure (PASP) calculated from the peak tricuspid regurgitation velocity by continuous wave Doppler as PASP= $4 \times (\text{peak velocity}_{TR}^2) + 5$.
2) Pulmonary artery pressure (PAP) indicated by (i) tricuspid regurgitation velocity (TRV)–time integral (mean value) and (ii) peak RV-RA gradient (systolic value).
3) PVR was estimated as $10 \times TRV/VTI_{RVOT}$.

- 3D echocardiography: (Analyses involving these variables are exploratory as it may be underpowered)

1) RVEF
2) RV free wall longitudinal strain (RVLS).

3) Right ventricular stroke volume (SV) was calculated as RV end-diastolic volume (EDV) – RV end-systolic volume (ESV).
4) Right ventricular function was assessed based on the RV fractional area change (RVFAC), calculated as (RV end-diastolic area – RV end-systolic area)/RV end-diastolic area and tissue Doppler-based tricuspid annular peak systolic velocity.
5) RV-PA coupling assessed as RVEF/PASP.

Outcome measurement

1. Incident AF through 2018 (ascertained from hospitalization codes and death certificates).
2. PAC frequency at Visit 6: number of PACs per hour (from the Zio patch report).
3. Frequency of SVT (per day), defined as 4 or more consecutive PACs.

Covariates (all at Visit 5)

- Demographic variables: age, sex, race-field center,
- Cardiovascular risk factors: systolic (SBP) and diastolic (DBP) blood pressures, BMI
- Cardiovascular conditions: coronary heart disease (CHD), heart failure (HF)
- Echocardiographic parameters: left atrial volume index (LAVi), left ventricular ejection fraction (LVEF), E/e′septal, peak LA strain
- Medications: beta blockers, calcium channel blockers, and other antiarrhythmic medications

Statistical analyses

- Analyses will be performed using SAS 9.4. Participant characteristics will be described using mean ± standard deviation for continuous variables, median (interquartile range) for highly skewed variables, and proportions for categorical variables.

- For H_1, Cox proportional hazards regression will be used to evaluate the associations between measures of pulmonary hemodynamics at Visit 5 with incident AF through 2018.

    - Model 1 will be adjusted for age at Visit 5, sex, race/center.
    - Model 2 will be additionally adjusted for LAVi, LVEF, E/e′septal, peak LA strain, SBP, DBP, and medications
    - Model 3: Model 2 + BMI, CHD, HF

  Proportional hazards assumption will be tested by using an interaction term between exposure variables and time. As sensitivity analyses, we will re-evaluate associations excluding participants with prevalent HF at Visit 5.

- For H2 and H3, we will examine the distributions of PAC and SVTs. We will log transform these variables as they tend to be highly skewed. Nearly all participants have PACs and SVTs (85%) and therefore, for those few who do not have a PAC or SVT we will assign

them a value of one run during their Zio XT ®Patch wear time. To assess the associations between pulmonary hemodynamics at visit 5 with PACs and SVTs at visit 6, we will construct linear regression models with robust standard errors and construct following models:

- Model 1 will be adjusted for age at Visit 5, sex, race/center.
- Model 2 will be additionally adjusted for LAVi, LVEF, E/e′septal, peak LA strain, SBP, DBP, and medications
- Model 3: Model 2 + BMI, CHD, HF

As sensitivity analyses, we will re-evaluate associations excluding participants with HF, and using inverse probability weighting for attrition due to Visit 6 non-attendance, death, or not wearing the Zio XT ®Patch.

Limitations

Echocardiographic measures of pulmonary hemodynamics are not uniformly available in the study sample. This may lead to selection bias. We will compare those with available pulmonary hemodynamic data to those with no data, and if important differences are noted, we will consider additional sensitivity analyses using inverse probability weighting. 2D Echocardiographic measures of pulmonary hemodynamics are not gold standard. Although they have been validated against invasive hemodynamic measures, they remain estimations and may result in misspecification of exposure. PH due to left heart disease is the most common type of PH, hence AF in the setting of PH is most commonly due to left heart disease. To mitigate the strong confounding by left heart disease, we are adjusting for echocardiographic indices of LV diastolic function (E/e'), LA vol index, and LA strain. Additionally, we will run sensitivity analyses excluding those with prevalent HF at Visit 5.

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)?

Nochioka K, Querejeta Roca G, Claggett B, et al. Right Ventricular Function, Right Ventricular-Pulmonary Artery Coupling, and Heart Failure Risk in 4 US Communities: The Atherosclerosis Risk in Communities (ARIC) Study. JAMA Cardiol. 2018;3(10):939–948. doi:10.1001/jamacardio.2018.2454

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 (list number* __2014.18 Chen_____)

___ 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.htmshows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication.Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu.I will be using CMS data in my manuscript ____ Yes __X No.

References:

1. Wanamaker B, Cascino T, McLaughlin V, Oral H, Latchamsetty R, Siontis KC. Atrial Arrhythmias in Pulmonary Hypertension: Pathogenesis, Prognosis and Management. Arrhythm Electrophysiol Rev. 2018;7(1):43–48. doi:10.15420/aer.2018.3.2
2. Melenovsky V, Hwang SJ, Lin G, Redfield MM, Borlaug BA. Right heart dysfunction in heart failure with preserved ejection fraction. Eur Heart J. 2014;35(48):3452–3462. doi:10.1093/eurheartj/ehu193
3. Simonneau G, Gatzoulis MA, Adatia I et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D34–41. Doi: 10.1016/j.jacc.2013.10.029.
4. Rajdev A, Garan H, Biviano A. Arrhythmias in pulmonary arterial hypertension. Prog Cardiovasc Dis. 2012;55(2):180–186.
5. Lam CS, Borlaug BA, Kane GC, Enders FT, Rodeheffer RJ, Redfield MM. Age-associated increases in pulmonary artery systolic pressure in the general population. Circulation. 2009;119(20):2663-2670.
6. Lakshmanan S, Jankowich M, Wu WC, Blackshear C, Abbasi S, Choudhary G. Gender Differences in Risk Factors Associated With Pulmonary Artery Systolic Pressure, Heart Failure, and Mortality in Blacks: Jackson Heart Study. J Am Heart Assoc. 2020;9(1):e013034. doi:10.1161/JAHA.119.013034
7. Kalogeropoulos AP, Siwamogsatham S, Hayek S, et al. Echocardiographic assessment of pulmonary artery systolic pressure and outcomes in ambulatory heart failure patients. J Am Heart Assoc. 2014;3(1):e000363. Published 2014 Feb 3. doi:10.1161/JAHA.113.000363
8. Nochioka K, Querejeta Roca G, Claggett B, et al. Right Ventricular Function, Right Ventricular-Pulmonary Artery Coupling, and Heart Failure Risk in 4 US Communities: The Atherosclerosis Risk in Communities (ARIC) Study. JAMA Cardiol. 2018;3(10):939–948. doi:10.1001/jamacardio.2018.2454