ARIC Manuscript Proposal #3948

PC Reviewed: 10/12/21 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Cardiac autonomic function as a predictor of incident COPD hospitalizations and lung function decline in the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Auton fxn and COPD in ARIC

2. Writing Group:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ___[DM]__ **[please confirm with your initials electronically or in writing]**

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3. Timeline:
Aug – Sep 2021: writing group and proposal development
Oct 2021: Initial data analysis
Nov 3rd, 2021: American Thoracic Society Abstract Deadline
Nov 2021 – May 2022: Manuscript preparation
Jun 2022: Manuscript submission

4. Rationale: Chronic obstructive pulmonary disease (COPD) is a common, progressive, respiratory condition that is characterized by expiratory airflow obstruction on spirometry, respiratory symptoms, and a history of chronic exposure to noxious stimuli such as cigarette smoke or air pollution (Singh 2019). Tobacco and biomass smoke exposure, aging, lower peak lung function in early adulthood, and genetics increase susceptibility to COPD but a significant proportion of the risk for COPD remains unexplained (Mannino 2007). Much of the morbidity and mortality attributable to COPD is characterized by periods of worsening respiratory symptoms known as acute exacerbations of COPD (AECOPD). Worse lung function, a history of previous exacerbations, and a greater burden of respiratory symptoms increase risk of AECOPD, but significant portions of this risk also remain unexplained (Hurst 2010). Autonomic dysfunction is common in COPD but has not been well studied as a risk factor for the development of COPD or for AECOPD.

The autonomic nervous system is divided into two arms, the sympathetic (i.e. fight or flight) and the parasympathetic (i.e. rest and digest). Together, these two arms maintain homeostasis and respond to changes in the environment (Shaffer 2017). The autonomic nervous system innervates virtually every organ system, including the lungs. Activation of the sympathetic nervous system leads to bronchodilation, and activation of the parasympathetic nervous system leads to bronchoconstriction and mucous production (Widdicombe 1970). Modulation of these effects with inhaled medications are the most used treatments for COPD. Direct measurement of autonomic nervous system activity is limited by the need for invasive microneurography sampling of sympathetic and parasympathetic nerve fibers. An alternate and widely accepted non-invasive method of quantifying autonomic function relies on control of the heart rate as a key autonomic function. Differences in time between heart beats, known as heart rate variability, allows non-invasive and repeated quantification of autonomic function in clinical and research settings.

Lower heart rate variability is associated with worse outcomes in general population cohorts and specific disease states such as cardiovascular disease, (Dekker 2000, Fyfe-Johnson 2016, Kubota 2017, Liao 2002, Maheshwari 2016), but has been under-investigated in relation to COPD. Numerous small ($n < 50$) studies have found that participants with COPD have lower heart rate variability than controls (reviewed in Mohammed 2015), but these associations have not been explored in a large general population sample. The etiology of this association is not entirely clear, but it is commonly hypothesized that COPD and lower lung function lead to lower heart rate variability through lung hyperinflation, lower physical activity, physiologic stress from lower lung function, medications, hypoxia, and systemic inflammation (Chhabra 2014, da la

Goulart 2017, Yuan 2019). However, it is also possible that autonomic dysfunction precedes the development of COPD. Orthostatic blood pressure changes are another non-invasive measure of autonomic function which have been cross-sectionally associated with COPD (Robertson 1998) Additionally, Ricci and colleagues found that subtle changes in orthostatic systolic blood pressure and resting heart rate in participants with normal spirometry at baseline were associated with incident hospitalization for COPD (by ICD codes) during 32 years of follow-up (Ricci 2018). They did not analyze lung function decline, and we are aware of no studies have done so.

Heart rate variability as a risk factor for AECOPD is also under studied. In a secondary analysis of a randomized clinical trial of participants with COPD, we found that the root mean square of sequential differences in normal RR intervals (RMSSD) on 10-second ECG may be associated with risk of hospitalization for AECOPD, but that study was limited by a short, 10-second clinical ECG, and relatively short follow up of 1 year (unpublished data). We are aware of no studies that have analyzed longer recordings of heart rate variability (which include more heart rate variability metrics and may better reflect autonomic nervous system activity) as a risk factor for COPD hospitalizations.

5. Main Hypothesis/Study Questions:

Study question 1: Are lower heart rate variability and orthostatic hypotension cross-sectionally associated with a higher baseline prevalence of COPD and decreased lung function [lower forced expiratory volume in 1-second (FEV_1)]?

Study question 2: Are lower heart rate variability and orthostatic hypotension at baseline associated with higher risk of incident hospitalization for COPD?

Study question 3: Are lower heart rate variability and orthostatic hypotension at baseline associated with faster lung function decline [forced expiratory volume in 1-second (FEV_1) and FEV_1/forced vital capacity (FVC) ratio]?

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 comparison (SQ1) and longitudinal cohort analysis (SQs 2 and 3)

Inclusion criteria: participants with baseline spirometry and at least one of: HRV measures from 2-minute ECG rhythm strip or orthostatic blood pressure measurements

Exclusion criteria: baseline spirometry does not meet quality standards, not Black or white and Black participants from the MN and MD centers (due to low numbers). We will also exclude participants with atrial fibrillation, atrial flutter, grade II or III AV block, pacemakers, supraventricular tachycardia, and ventricular tachycardia.

Primary exposure variables:

1. Heart rate variability measures from 2-minute rhythm strip at visit 1 (Liao 1995, Liao 2002, Agarwal 2017)
    a. Time domain: standard deviation of RR intervals (SDNN), root mean square of successive differences of RR intervals (RMSSD), mean of all normal RR intervals.
    b. Frequency domain: Low frequency (LF) and high frequency (HF) power and LF/HF ratio.

2. Orthostatic hypotension from baseline visit (Rawlings 2018). This will be calculated as the average of the supine blood pressure measurements minus the average of the standing blood pressure measurements (including the first measurement upon standing) (Rose 2006).
    a. A drop in systolic blood pressure (BP) of at least 20 mm Hg or a drop in diastolic BP of at least 10 mm Hg on standing.
    b. Change in systolic blood pressure (though typically analyzed dichotomously as in (a), previous analyses including Ricci 2018 and Rawlings 2018 have also analyzed orthostatic change in blood pressure as a continuous variable)
    c. Change in diastolic blood pressure

Outcomes:

Study Question #1: Lung function at baseline

a. Prevalent COPD
b. Prevalent preserved ratio impaired spirometry (PRISm)
c. FEV1
d. FEV_1/FVC

Study Question #2: COPD related hospitalization (Validated in Oelsner 2016 and Oelsner 2018, previously used in ARIC Bhatt 2019 – ICD code can be in any diagnosis field)

e. COPD (ICD-9 496 and ICD-10 J44)
f. Chronic bronchitis (ICD-9 490-491 and ICD-10 J40-J42)
g. Emphysema (ICD-9 492 and ICD-10 J43)

Study Question #3: Lung function decline from pulmonary function testing at visits 1, 2, and 5 (Mirabelli 2016: inverse probability weighted independence estimating equations with population averaged linear models for regression conditioned on being alive. We've also used repeated-measures mixed models with random within person intercept and slope to model lung function decline, Kunisaki 2016).

h. FEV_1 slope
i. FEV_1/FVC slope

Baseline variables:

1. Age
2. Sex
3. Race-Center (5-level variable)
4. Medications

    a. Inhalers
    b. Beta blockers and calcium channel blockers
    c. Anti-arrhythmics (including digoxin)
5. Height, BMI
6. Smoking status (current, former, never)
    a. Pack years of smoking for current and former smokers
7. Respiratory symptoms
    a. Cough (yes to RPAA01, RPAA02, RPAA03, or RPAA04)
    b. Phlegm (yes to PRAA07, RPAA08, RPAA09, or RPAA10)
    c. Dyspnea (yes to RPAA21, RPAA22, RPAA23, or RPAA24)
    d. Recurrent chest infections (yes to RPAA19)

Statistical analysis:

Study question 1: Are lower heart rate variability and orthostatic hypotension cross-sectionally associated with a higher prevalence of COPD and decreased lung function [forced expiratory volume in 1-second (FEV_1)] in a general community-based cohort?

a. Using logistic regression, test associations between heart rate variability measures, orthostatic hypotension, and the presence or absence of COPD ($FEV_1/FVC < 0.7$). Using the same method, test alternative definitions of COPD (spirometry + $\geq$ 10 pack years smoking, spirometry + $\geq$ 10 pack years smoking + respiratory symptoms).
b. Using linear regression, test associations between heart rate variability measures, orthostatic hypotension, and FEV_1 as a continuous measure.
c. Nested models will be used. Model 1 will adjust for age, sex, height, and race-center. Model 2 will additionally adjust for smoking status and pack years. Model 3 will further adjust for BMI.
d. Perform the above analyses excluding participants on beta-blockers, calcium channel blockers, or anti-arrhythmics.
e. Test for interactions by sex by including cross-product terms in the models.

Study question 2:
Are lower heart rate variability and orthostatic hypotension at baseline associated with a higher risk of incident hospitalization for COPD?

a. Using Cox-proportional hazards models, do baseline heart rate variability measures or orthostatic hypotension predict time to first COPD related hospitalization.
b. Nested models will be used, as noted in 1c.
c. Stratify analyses by COPD vs no COPD at baseline (though our primary question is whether abnormal autonomic dysfunction precedes the clinical presentation of COPD, predictors of hospitalization in those with COPD are also relevant)
d. Perform the above analyses excluding participants on beta-blockers, calcium channel blockers, or anti-arrhythmics.
e. Test for interactions by sex by including cross-product terms in the models.
f. For models where OH is the primary exposure, we will also explore the impact of adjusting for HR.

Study question 3: Are lower heart rate variability and orthostatic hypotension at baseline associated with faster lung function decline (FEV_1 or FEV_1/FVC ratio)?

a. Similar to Mirabelli 2016, use inverse probability weighted independence estimating equations with population averaged linear models for regression conditioned on being alive. We've also used repeated-measures mixed models with random within person intercept and slope to model lung function decline, Kunisaki 2016)
b. Nested models will be used, as noted in 1c.
c. Perform the above analyses excluding participants on beta-blockers, calcium channel blockers, or anti-arrhythmics.
d. Stratify by COPD vs no COPD at baseline.
e. Test for interactions by sex by including cross-product terms in the models.
f. For models where OH is the primary exposure, we will also explore the impact of adjusting for HR.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes x No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 current derived consent file ICTDER05 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/aricproposals/dtSearch.html

___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)?

None directly relevant. COPD has been exposure in many manuscripts, but relatively few have explored COPD as an outcome (and none with an exposure similar to HRV).

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __X__ 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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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.

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