ARIC Manuscript Proposal #4178

PC Reviewed: 12/13/22 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Associations between two-week heart rate variability recordings and respiratory health outcomes in the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): HRV and resp health 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

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3. Timeline:
Oct – Dec 2022: writing group and proposal development
Dec 2022 – Jan 2023: Initial data analysis
Feb 2022 – June 2023: Manuscript preparation
July 2023: Manuscript submission

4. Rationale:
Chronic obstructive pulmonary disease (COPD) afflicts approximately 6% of the population of the United States.[1] COPD is defined by incompletely reversible airflow obstruction on spirometry, chronic respiratory symptoms, and a history of exposure to noxious stimuli, such as tobacco smoke or air pollution.[2] There are additional risk factors for COPD, such as lower peak lung function, poverty, and maternal smoking that are not incorporated into this definition, but much of the risk remains unexplained.[3,4] These other risk factors are likely to take on increasing importance as smoking rates decrease. Acute exacerbations of COPD (AECOPD) lead to much of the morbidity and mortality among people with COPD. Known risk factors include worse lung function, a history of previous exacerbations, and a greater burden of respiratory symptoms, but significant portions of this risk also remain unexplained.[5] Autonomic dysfunction is common in COPD, but has been relatively under investigated as a risk factor for COPD and AECOPD.

The autonomic nervous system (ANS) innervates every organ system in the body, maintains physiologic homeostasis, and responds to changes in the environment.[6] The ANS has important effects on the lungs, particularly with regard to COPD. Activation of the sympathetic arm of the ANS leads to bronchodilation, while activation of the parasympathetic arm leads to bronchoconstriction and increased mucous production.[7] These effects are leveraged for treatment in COPD, where inhaled beta agonists (sympathomimetics) are used for bronchodilation, and parasympathetic antagonists are used to block bronchoconstriction and decrease mucous production.[2] Direct measurement of ANS activity is not feasible as it requires invasive and highly technical techniques, but the ANS also controls the variation in time between heart beats, which is known as heart rate variability (HRV). HRV can be measured non-invasively and is used in research and clinical settings as an accepted method of ANS quantification.

Lower heart rate variability is associated with worse outcomes in general population cohorts, and specific disease states such as cardiovascular disease.[8–11] Multiple measures of autonomic dysfunction, including HRV, have been shown to be abnormal in COPD.[12] However the studies exploring this association have been small (n<50) and publication bias is possible. The etiology of the association between lower heart rate variability and COPD is unknown, but one possibility is chronic sympathetic activation as a result of chronic airflow obstruction, hypoxia, medications, and inflammation.[13,14] In addition to lower HRV, chronic sympathetic activation could also lead to downregulation of beta receptors in the lungs, and decreased response to be beta-agonists. Measurement of the response to beta-agonists is known as bronchodilator reversibility.

Compared to other disease states there is less known about the prognostic implications of HRV in COPD. We recently presented that lower HRV was associated with a higher risk of COPD hospitalization over 25 years of follow-up using data from the baseline visit in ARIC (manuscript under review by publications committee). That analysis was limited by the fairly brief, 2-minute resting ECGs available from the baseline visit. Longer ECGs, such as the 2-week Zio patches from visit 6 in ARIC, capture HRV during various states of exertion, at various times of day, and allow for additional HRV measurements such as very-low-frequency ultra-low-frequency power, which may have a stronger association with all-cause mortality than HRV measures available from shorter ECGs.[6]

5. Main Hypothesis/Study Questions:

Study question 1: Is lower HRV cross-sectionally associated with a higher prevalence of self-reported obstructive lung disease?

Study question 2: Is lower HRV associated with decreased lung function [forced expiratory volume in 1-second(FEV_1), forced vital capacity (FVC), and their ratio (FEV_1/FVC)] from the prior visit?

Study question 3: Is lower HRV associated with less bronchodilator reversibility?

Study question 4: Is lower HRV associated with a higher risk of incident COPD hospitalization?

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), quasi-cross sectional comparison (SQ2 and SQ3), and longitudinal prospective cohort analysis (SQ 4)

Inclusion criteria: participants with HRV measurements from Ziopatch at visit 6.

Exclusion criteria: Not Black or white and Black participants from the MN and MD centers (due to low numbers). For SQs 2 and 3 we will additionally exclude participants with low quality spirometry.

Primary exposure variables:

1. Heart rate variability measures from 14-day Ziopatch at visit 6
    a. SDNN (standard deviation of NN intervals)
    b. RMSSD (root mean square of successive differences between normal heartbeats)
    c. LF (low frequency power)
    d. HF (high frequency power)

e. LF/HF ratio

Outcomes:

Study Question #1: Self-reported obstructive lung disease

a. COPD
b. Asthma

Study Question #2: Lung function from visit 5.

a. Post-bronchodilator FEV_1
b. Post-bronchodilator FVC
c. Post-bronchodilator FEV_1/FVC

Study Question #3: Bronchodilator reversibility

a. Absolute FEV_1 change (post-bronchodilator FEV_1 minus pre-bronchodilator FEV_1)
b. Absolute FVC change (post-bronchodilator FVC minus pre-bronchodilator FVC)
c. Categorical bronchodilator reversibility (12% and 200 mL increase in FEV_1 and/or FVC)

Study Question #4: Incident COPD hospitalizations from hospital discharge (any diagnosis field).

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

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

Statistical analysis:

Study question 1: Is lower HRV cross-sectionally associated with a higher prevalence of self-reported obstructive lung disease?

a. Using logistic regression, test associations between each log-transformed HRV measure and the presence or absence of COPD and asthma.
b. 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. Model 4 will adjust for beta-blocker, calcium channel blocker, and anti-arrhythmic use.

c. Test for interactions by sex and medication use (beta-blocker, calcium channel blocker, and anti-arrhythmics) by including cross-product terms in the models.

Study question 2: Is lower HRV associated with decreased lung function [forced expiratory volume in 1-second (FEV_1), forced vital capacity (FVC), and their ratio (FEV_1/FVC)] from the prior visit?

a. Using linear regression, test associations between log-transformed HRV measures and lung function (FEV_1, FVC, and FEV_1/FVC ratio).
b. Nested models will be used as in 1b.
c. Interactions will be tested as in 1c.
d. Based upon results from the previous HRV/COPD analysis (#3948), stratify analyses by baseline airflow obstruction ($FEV_1/FVC < 0.7$).

Study question 3: Is lower HRV associated with lower bronchodilator reversibility?

a. Using linear regression test associations between log-transformed HRV measures and absolute changes in FEV_1, FVC, and FEV_1/FVC ratio.
b. Using logistic regression test associations between log-transformed HRV measures and categorical bronchodilator reversibility.
c. Nested models will be used as in 1b.
d. Interactions will be tested as in 1c.
e. Stratified analyses will be performed as an 2d.

Study question 4: Is lower HRV associated with a higher risk of incident COPD hospitalization?

a. Using Cox-proportional hazards models, test associations between log-transformed HRV measures and time to first COPD hospitalization. The proportional hazards assumption will be tested.
b. Nested models will be used as in 1c.
c. Interactions will be tested as in 1c.
d. Stratified analyses will be performed as an 2d.

<u>Anticipated Methodologic Challenges</u>

Study questions 2 and 3 will use a quasi-cross sectional design, with lung function measurements coming before HRV measurements. This is not ideal. However, the data are very unique, and both lung function measurements and HRV measurements would be expected to be correlated within the (counterfactual) measurements at the visit where the data was not collected.

Study question 4: Precision may be poor for this analysis. If after getting the HRV data we realize that this analysis is not feasible for power issues, we will not proceed with testing this hypothesis.

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/aric/mantrack/maintain/search/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)?

We previously analyzed the association between HRV and incident COPD hospitalizations using HRV data from the baseline visit (#3948). There are no other directly related proposals.

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___)
___ 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.

References:

1. Biener AI, Decker SL, Rohde F. Prevalence and Treatment of Chronic Obstructive Pulmonary Disease (COPD) in the United States. JAMA. 2019 Aug 20;322(7):602. PMID: 31429884

2. Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, Criner GJ, Frith P, Halpin DMG, Han M, López Varela MV, Martinez F, Montes de Oca M, Papi A, Pavord ID, Roche N, Sin DD, Stockley R, Vestbo J, Wedzicha JA, Vogelmeier C. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: the GOLD science committee report 2019. Eur Respir J. 2019 May;53(5):1900164.

3. Postma DS, Bush A, van den Berge M. Risk factors and early origins of chronic obstructive pulmonary disease. The Lancet. 2015 Mar;385(9971):899–909.

4. Svanes C, Sunyer J, Plana E, Dharmage S, Heinrich J, Jarvis D, de Marco R, Norback D, Raherison C, Villani S, Wjst M, Svanes K, Anto JM. Early life origins of chronic obstructive pulmonary disease. Thorax. 2010 Jan 1;65(1):14–20.

5. Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, Miller B, Lomas DA, Agusti A, MacNee W, Calverley P, Rennard S, Wouters EFM, Wedzicha JA. Susceptibility to Exacerbation in Chronic Obstructive Pulmonary Disease. N Engl J Med. 2010 Sep 16;363(12):1128–1138. PMID: 20843247

6. Shaffer F, Ginsberg JP. An Overview of Heart Rate Variability Metrics and Norms. Front Public Health. 2017 Sep 28;5:258. PMCID: PMC5624990

7. Widdicombe JG, Sterling GM. The autonomic nervous system and breathing. Arch Intern Med. 1970 Aug;126(2):311–329. PMID: 4247101

8. Dekker JM, Crow RS, Folsom AR, Hannan PJ, Liao D, Swenne CA, Schouten EG. Low Heart Rate Variability in a 2-Minute Rhythm Strip Predicts Risk of Coronary Heart Disease and Mortality From Several Causes: The ARIC Study. Circulation. 2000 Sep 12;102(11):1239–1244. PMID: 10982537

9. Fyfe-Johnson AL, Muller CJ, Alonso A, Folsom AR, Gottesman RF, Rosamond WD, Whitsel EA, Agarwal SK, MacLehose RF. Heart Rate Variability and Incident Stroke: The Atherosclerosis Risk in Communities Study. Stroke. 2016 Jun;47(6):1452–1458. PMCID: PMC4880420

10. Kubota Y, Chen LY, Whitsel EA, Folsom AR. Heart rate variability and lifetime risk of cardiovascular disease: the Atherosclerosis Risk in Communities Study. Annals of Epidemiology. 2017 Oct;27(10):619–625. PMCID: PMC5821272

11. Maheshwari A, Norby FL, Soliman EZ, Adabag S, Whitsel EA, Alonso A, Chen LY. Low Heart Rate Variability in a 2-Minute Electrocardiogram Recording Is Associated with an Increased Risk of Sudden Cardiac Death in the General Population: The Atherosclerosis Risk in Communities Study. Talkachova A, editor. PLoS ONE. 2016 Aug 23;11(8):e0161648. PMCID: PMC4995012

12. Mohammed J, Meeus M, Derom E, Da Silva H, Calders P. Evidence for Autonomic Function and Its Influencing Factors in Subjects With COPD: A Systematic Review. Respir Care. 2015 Dec;60(12):1841–1851. PMID: 26487747

13. González-Costello J, Armstrong HF, Jorde UP, Bevelaqua AC, Letarte L, Thomashow BM, Bartels MN. Chronotropic incompetence predicts mortality in severe obstructive pulmonary disease. Respiratory Physiology & Neurobiology. 2013 Aug;188(2):113–118. PMCID: PMC4495898

14. Zamarrón C, Lado MJ, Teijeiro T, Morete E, Vila XA, Lamas PF. Heart rate variability in patients with severe chronic obstructive pulmonary disease in a home care program. Technol Health Care. 2014;22(1):91–98. PMID: 24561881