ARIC Manuscript Proposal #3662

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1.a. Full Title: Decline in pulmonary function and arterial stiffness

b. Abbreviated Title (Length 26 characters): Lung function and aortic stiffness

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

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3. Timeline: Estimated 8 mos.

4. Rationale:
About 14% of US adults have some impairment of lung function, which is associated with an increased risk of cardiovascular (CV) events and cardiovascular related mortality.[1,2] Lung function may be altered due to smoking, air pollution exposure, and respiratory disease among other causes, and may be linked to cardiovascular disease indirectly through these exposures or through associated mechanisms such as chronic inflammation, comorbidity, or lung-heart hemodynamic interaction.[3–5] Arterial stiffening, caused by loss of elastin fibers, inflammation, accumulation of collagen fibers, or other mechanisms of arterial remodeling, is also a risk factor for CV events and damage to end organs.[6,7] While poor lung function and arterial stiffening are both associated with cardiovascular outcomes, the relationship between poor lung function and arterial stiffness remains undefined.

Most prior studies of lung function and arterial stiffening have been cross sectional, with mixed evidence for an association between poor pulmonary function and arterial stiffness. No significant association between quartiles of forced expiratory volume in one second (FEV1), a measure of lung function, and arterial stiffness was found in one cross-sectional study of a population free of chronic obstructive pulmonary disease (COPD).[8] However, another cross-sectional study found an association between FEV1 and arterial stiffness, but not forced vital capacity (FVC). This study also reported no connection between either FEV1, FVC, or arterial stiffness with markers of systemic inflammation, interleukin-6 and C-reactive protein.[9] Okamoto et al. examined decline in lung function over time reporting that a 5-year decline in lung function was associated with higher measures of arterial stiffness. No evidence for mediation by inflammatory agents was found.[10] Baseline poor pulmonary function was also found to be positively associated with subsequent 5-year change in central artery stiffness.[10] Measures of FEV1 and FVC from 20 years prior were determined to be better predictors of arterial stiffness in a sample of men than cross-sectional measures of lung function, demonstrating the importance of temporality in this potential relationship.[11] Most evidence points to an association between poor pulmonary function and arterial stiffness, but few address the relationship prospectively or in terms of worsening lung function. Although some of these studies attempted to investigate underlying pathophysiological processes that may link the two, the causal mechanisms are still unknown.

Several biological mechanisms have been proposed that may connect poor lung function and arterial stiffening. One involves a chronic systemic inflammation. Systemic inflammation has been reproducibly associated with chronic lung disease and impaired lung function, and moderately associated with aortic stiffening, but whether systemic inflammation is antecedent to impaired lung function and central arterial remodeling, or rather a systemic response to inflammatory processes in these organs, remains unclear.[12] Hypertension may also be a link. Animal model studies suggest that arterial stiffening precedes increasing blood pressure, although the association may be bi-directional, while epidemiologic findings show that reduced lung function is predictive of increased systolic blood pressure later in life.[7,13] Therefore, poor lung function and arterial stiffness may co-occur and jointly increase the risk of cardiovascular disease. Similarly, poor pulmonary function and arterial stiffness may be risk factors for diabetes, or diabetes may mediate this relationship. Some studies have proposed reduced lung function to be a risk factor for diabetes while others have found evidence of diabetes to be predictive of impaired lung function.[14] Multiple studies suggest a cross-sectional association between arterial stiffening and diabetes mellitus and indicate that arterial stiffening may be a consequence of diabetes mellitus or may occur simultaneously with the disease.[15] The mediating relationship of diabetes may be explained by chronic low-grade systemic inflammation or through autonomic neuropathy, both linked with diabetes, reduced lung function, and arterial stiffening.[15] Alternatively, lung function decline and artery wall remodeling may merely co-occur with increasing age or share an unknown common cause.[16] Lastly, aortic stiffening may be indicative of stiffening of the pulmonary vasculature or vice versa. Although many underlying pathophysiological processes and mechanisms have been proposed, none have been convincingly identified.

We propose to test the hypothesis that poor lung function at baseline and declining lung function over time, measured by forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) are associated with later central arterial stiffness measured by carotid-femoral pulse wave velocity (cfPWV) in the ARIC study population. We will characterize these associations by sex, race, and smoking status. Further, we will assess whether these

associations differ by type 2 diabetes or respiratory muscle strength, approximated by maximal inspiratory pressure (MIP) at visit 2.

5. Main Hypothesis/Study Questions:

Research aim: Investigate whether a) poor lung function at midlife or b) the rate of decline in lung function over time is positively associated with later-life central arterial stiffness.

1.1 Estimate the association between a) forced vital capacity (FVC) at visit 1 and b) change in FVC from visit 1 to visit 5, with carotid-femoral pulse wave velocity (cfPWV) at visit 5.

1.2 Estimate the association between a) forced expiratory volume in one second (FEV1) at visit 1 and b) change in FEV1 from visit 1 to visit 5, with cfPWV at visit 5.

1.3 Characterize these associations by sex, race, and smoking status.

1.4 Assess effect-measure modification of the associations of FVC and FEV1 with cfPWV by maximal inspiratory pressure (MIP) at visit 2, and by type 2 diabetes.

6. Design and analysis

This prospective, longitudinal cohort study will include all participants with measures of FEV1 and FVC at ARIC visits 1, 2 and 5, and cfPWV measures at visit 5. All demographic characteristics and medical histories were collected at visit 1.

Exclusions

Participants with missing lung function data from visits 1, 2 or 5, or with missing arterial stiffness data from visit 5. Participants with COPD and emphysema ascertained by hospital discharge diagnoses. Non-white and non-African American participants. Severely obese participants (BMI>40). Other arterial stiffness exclusions recommended by the ARIC PWV working group.

Lung capacity and expiratory function

Lung capacity will be assessed by FVC, the total volume of air that can be inhaled in milliliters. How quickly that air can be released, expiratory function, will be estimated by FEV1. FVC and FEV1 at visits 1 and 2 were collected using the Collins Survey II water-seal spirometer from the Warren E. Collins Company (Braintree, MA). At visit 5 the SensorMedics model 1022 dry-rolling seal volume spirometer (OMI, Houston, TX) was used. The highest measure out of three acceptable spirogram trials was selected for both FVC and FEV1. Change in lung capacity and expiratory function for descriptive statistics will be calculated by subtracting FVC and FEV1 at visit 5 from their corresponding measures at visit 1. Extensive quality control programs were in place and all lung function measurements were interpreted at a central reading site.

Central arterial stiffness

Central arterial stiffness will be approximated by cfPWV, considered the gold standard for measuring arterial stiffness.[17] cfPWV at visit 5 was measured using the Omron VP-100 plus system. Carotid-femoral distance, assessed using the Rosscraft Anthropometric Segmometer,

was calculated by subtracting 1) the distance from suprasternal notch to the recording site of the carotid artery from 2) the distance between the carotid artery and femoral artery recording sites. This distance was divided by the transit time of the pulse waveform, resulting in the final cfPWV measure. Arterial stiffness measurement was repeated once and averaged to ensure data quality. Quality control programs were in place, including an ongoing overview of a random sample of study measurements by a central site with feedback to study technicians.

Variables of Interest

Exposures: lung capacity and expiratory function measures (continuous and quartiles)

1. Forced vital capacity (FVC) at visit 1 and change in FVC across visits 1, 2 and 5
2. Forced expiratory volume in one second (FEV1) at visit 1 and change in FEV1 across visits 1, 2 and 5

Outcome: central arterial stiffness measured by carotid-femoral pulse wave velocity (cfPWV), continuous and quartiles

Covariates:

1. Smoking status (current, former, never; pack-years)
2. Sex
3. Race-center
4. History of asthma (self-report)
5. History of chronic lung disease (self-report, for exclusion)
6. COPD by hospital discharge ICD codes
7. Emphysema by hospital discharge ICD codes
8. BMI (for exclusion of severely obese persons)
9. Mean arterial pressure
10. Heart rate
11. Type 2 diabetes
12. Physical activity

Statistical Evaluation:

Both lung function, change in lung function (between visits 1 and 5), and arterial stiffness measures will be assessed continuously and by quartiles.

Descriptive statistics of continuous arterial stiffness at visit 5, demographic, and clinical measures will be examined by quartiles of change in FEV1 and FVC, and by FEV1 and FVC at baseline to explore non-linear associations. Additionally, we will produce descriptive statistics of continuous lung function longitudinal difference and baseline measures, demographic, and clinical measures by quartiles of cfPWV at visit 5 to assess potential non-linear trends. These descriptive analyses will be further stratified by smoking status, sex, and race-center.

We will examine the roles of death as a potential competing cause and of potential bias due to attrition after, characterizing the cohort by at baseline, those participants present at visit 5, participants lost to follow-up, and deceased participants. Descriptive analyses of baseline FEV1 and FVC, demographic, and clinical measures will be examined produced by participant status (alive, dead, lost to follow-up) at visit 5.

A. Baseline Measures of Lung Function

Estimate the association of FEV1 and FVC at baseline separately with cfPWV at V5 (adjusted, weighted linear regression models with "weights" to account for informative missingness…)

Predict 'aortic stiffness,' defined as the upper 75th percentile of cfPWV at V5 from baseline FEV1 and FVC (logistic or log-linear regression) adjusted for potential confounders including history of asthma, mean arterial pressure, heart rate, and diabetes. Effect estimates will be stratified by smoking, race-center and sex.

Effect measure modification posited a priori: maximum inspiratory muscle strength (MIP) at visit 2; type 2 diabetes (time-varying).

B. Age-related Decline in Lung Function

We will use a retrospective approach to assess the patterns of change in FVC and FEV1 by distribution-based strata of cfPWV at visit 5, and estimate adjusted, population-averaged values of change in FEV1, FVC at different ages (not exam visits), for strata of cfPWV at V5.

We will follow the analytic approach developed by Mirabelli MC, Preisser JS et al.[16] to estimate temporal change in lung function (http://dx.doi.org/10.1016/j.rmed.2016.02.003). Inverse-probability-weighted estimating equations conditioning-on-being-alive will be used to estimate annual population-averaged mean changes in FEV1 and FVC by race, sex, and smoking status. cfPWV stratum-specific patterns of intra-individual change in pulmonary function test will be calculated for ages 45, 60, 75 by quantiles of cfPWV, conditional on being alive at that age. The age category-specific slopes and variances of intra-individual change in FEV1 and FVC estimates will be contrasted by strata of cfPWV to characterize (and test for) variation in lung function decline by level of cfPWV in older adulthood. The analyses will be done by smoking status, sex and race. They will be further assessed for effect measure modification by MIP and type 2 diabetes.

At each cohort examination point weights will be derived based on predicted probabilities of each participant to continue to participate in the ARIC study conditioning on his/her being alive. These predicted probabilities will then be applied to up-weight the contribution of participants with demographic and health-related characteristics of those not observed due to non-death dropout. An occurrence of COPD, emphysema at baseline, ascertained through hospital discharge ICD codes, will be incorporated in the computation of the inverse probability weights.

<u>Limitations</u>:
Measures of arterial stiffness were not collected before visit 5, therefore we cannot observe the change in arterial stiffness that may be concurrent with change in lung function. A further limitation is the availability of only three repeat measures of lung function, the first two proximal to the baseline and the third approximately 25 years later. These measurements were taken using two different devices (the Collins Survey II water-seal spirometer at visits 1 and 2 and the SensorMedics model 1022 dry-rolling seal volume spirometer at visits 5). The comparability of measurements from these two devices has not been previously studied. Other studies comparing spirometry measures from different instruments found that the main sources of variability were related to the individual participants and technicians, with variability stemming from differences between instruments generally being small and fixed.[18] A meta-analysis of spirometry measures from eight different cohort studies classified 88.4%, 91.2%,

and 89.5% of ARIC spirometry measures as valid measurements (reproducibility of the two largest lung volumes within 150 mL) from visits 1, 2, and 5 respectively.[19] Another limitation is the racial distribution of participants by study sites. Most of the African American participants in this population reside in Jackson, Mississippi, making study center highly correlated with race, which requires the use of race-center as a covariate. The possibility of residual confounding cannot be ruled out.

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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)?

None found

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* _AS 2015-23**_)**

___ 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.