ARIC Manuscript Proposal #1377

1. a. Full Title: Relationship between pulmonary disease, lung function and incident hospitalized heart failure: The Atherosclerosis risk in communities (ARIC) study

b. Abbreviated Title (Length 26 characters): Lung function and heart failure

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __SKA__

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3. Timeline: Approval of this manuscript by the ARIC Publications Committee will then enable work on this manuscript. Once started, this work will lead to manuscript(s) within 15 months.

4. Rationale: Heart Failure (HF) is a major public health problem in the US [1] while it has a grim prognosis (30% mortality at one year)[2], its cost of treatment exceeds those for both coronary artery disease and cancer combined accounting for about 5.4% of the total US health care cost [3].

HF is a common comorbidity among patients with chronic obstructive airway disease (COAD), and vice versa [4, 5]. Both of the above conditions may present with symptoms of dyspnea and orthopnea. Furthermore, evidence of airway obstruction and bronchodilator response on pulmonary function testing may be evident not only in COAD but also in HF[6]. Thus, COAD complicates both the diagnosis and treatment of heart failure. Recent research has shown that immunization with the influenza (a disease mainly affecting the lungs) vaccine prevents new onset of heart failure [7]. However, little literature is available about the relationship between lung disease (and functional state) with incident heart failure.
Several studies have reported higher cardiovascular mortality among individuals with lower lung function and COAD. Factors such as chronic muscle wasting, autonomic dysfunction, systemic inflammation[8], or oxidative stress may be responsible for this increased risk. [9] To the best of our knowledge, there is no literature on existing COPD diagnosis and risk of incident hospitalized HF.

Lung function is typically assessed using standardized spirometry determined forced vital capacity (FVC), forced expiratory volume during initial 1 second duration (FEV1) and their ratio (FVC/FEV1). Vital capacity (VC) is reduced during decompensated HF and its measurement is recommended to evaluate response to therapy[10]. However, there is no mention of lung disease/assessment for risk stratification or management in the recent ACC/AHA guidelines for HF [11]. Further, little is known about the risk of heart failure in individuals with reduced lung function (vital capacity (height adjusted), FEV1, FEV1/FVC).

A study by Kannel et al, found that vital capacity is an indirect marker of left ventricular performance. It is decreased in individuals with left ventricular dysfunction (LVD) possibly due to weakness of respiratory muscles, increase in lung fluid, adverse changes in lung mechanics (decreased compliance or a large closing volume), and increase in myocardial mass without a concomitant rise in central and pulmonary vascular blood volume[12]. In the above study, reduced FVC, but not obstructive lung disease as defined by reduced FEV1/total VC, was found to be associated with incident heart failure[12]. Other studies have shown that reduced FEV1[13], peak expiratory flow rate[14] are associated with incident HF. To some extent, the above associations might reflect misclassification of dyspnea due to lung disease as CHF, as well as the concordance of age-related decrease in pulmonary function with increases in incident CHF.

In addition to aging, a few risk factors such as smoking, obesity, anemia and air pollution (high particulate matter concentration), have adverse effect on both lung function and CAD risk. In addition, beta blockers which are used to treat heart failure, may exacerbate symptoms of underlying COPD.

The effect of smoking in the causation of CAD and subsequent systolic HF has been documented. Cigarette smoking may act through other pathways leading to damage to the lung parenchyma further leading to pulmonary hypertension, and diastolic heart failure. This is supported by a study showing a greater decline in FEV1 among lifelong smokers as compared to never-smokers [15]. In the study by Kannel et al, association between lung function and incident HF existed even after adjustment for smoking [12]. A recent ARIC study showed greater decline in lung function in diabetics as compared to non-diabetics implicating blood sugar dysregulation in causing lung injury[16].

In addition to increasing the risk of incident CAD and subsequent systolic heart failure; obesity may predispose to diastolic dysfunction[17, 18] and subsequent CAD and heart failure via sleep-disordered breathing (intermittent hypoxemia, hypertension and arrhythmias (atrial fibrillation))[19].

Air pollution (PM) is associated with lower heart rate variability and higher levels inflammatory markers, and increased CVD related mortality in the ARIC cohort.

Also, anemia is common in patients with COAD and is associated with increased risk of incident HF.
Vital capacity shows weak negative correlation with blood sugar, blood pressure, serum cholesterol and heart enlargement especially in the elderly [20]. The strongest correlation was seen with handgrip muscle strength[20]. Also, higher FEV1 has been associated with favorable cardiovascular risk profile (BP, T2DM, cholesterol, fibrinogen, WBC, and BMI)[21, 22]. Low VC is also associated with incident diabetes[22, 23], left ventricular hypertrophy[24], sub-clinical atherosclerosis (measured by ankle-brachial index and intima-media thickness)[25], and incident ischemic cardiac disease [8, 24, 26-28].

The goals of this proposal are to assess the relationship between chronic lung disease, lung function and incident HF. Since there may be a differential relationship by race, the ARIC cohort provides an opportunity to explore the higher risk of HF seen in African Americans in the framework outlined above. Also, socio-economic status (confounded by race in ARIC), may be an important determinant of lung function and the lung function-heart failure relationship. We expect this relationship to differ by co-morbidities and to be attenuated by adjustment for variables possibly on the causal pathway. This relationship (if present) may help in risk stratification, improve understanding of biologic mechanisms and may provide evidence for research to further understanding of the lung-heart relationship and preventive strategies. We hypothesize that poor lung function at study baseline in individuals without HF is associated with increased risk of subsequent HF; this relationship is stronger in those with CAD, smokers, and those with diabetes; and will be attenuated after adjustment for inflammatory, pro-coagulability and metabolic derangement markers.

5. Main Hypothesis/Study Questions:
The following questions will be addressed with special attention to race and gender.

1. Estimate the proportion of individuals with HF (self reported HF and incident hospitalized HF) who have prevalent COAD in general population.

2. Quantify the association of COAD (self reported and GOLD classification) at study baseline with increased risk of incident hospitalized HF.
   a. The above relation is modified by smoking, obesity and baseline comorbidity (CAD and Diabetes), individually.

3. Estimate the association of lung function (FVC, FEV1, and FEV1/FVC, after appropriate adjustments for gender and height) with risk of incident hospitalized HF.
   a. The above relation is modified by smoking, obesity and baseline comorbidity (CAD and Diabetes).
   b. The above relationship exists in the subset of cohort without CAD prior to incident HF.
   c. The above relation becomes weaker after adjusting for potential markers of inflammation, hypercoagulability, SES, maximal inspiratory pressure (MIP) available in ARIC cohort, as these may be intermediary in the observed association.

4. Individuals with greater decline in lung function (between visit 1 and visit 2) are at higher risk of incident hospitalized HF after adjusting for baseline function (visit 1).
**Analytical methods:**
Proportions of individuals with heart failure and respiratory comorbidity will be reported both at ARIC cohort baseline visit (self reported) and at first hospitalization with heart failure (ICD codes). Prevalent HF will be defined as the reported current intake of HF medication at the baseline examination (n = 83) or evidence of manifest HF as defined by the Gothenburg criteria stage 3 (n = 669), which require the presence of specific cardiac and pulmonary symptoms as well as medical treatment of HF[14]. By January 1st, 2003, 1193 study participants met these incident HF criteria. Analyses for this study will include additional incident HF events i.e., through 2004. Those who had incident HF mentioned in the death certificate (n= 78) will be included in a sub-analysis (as their characteristics may be different, HF due to circulatory collapse, sepsis etc.)

Cox proportional hazards regression models will be used to assess the relationship between lung disease (self reported and modified GOLD classification) and incident HF. Racial and gender differences will be explored in subgroup analysis. Also, effect modification will be examined for smoking and other comorbidity. At study baseline there were 54% never-smoker women and 30% never smoker men.

Similarly, Cox regression models will be used to examine the relationship between functional measures FVC, FEV1 (divided by quartiles) and incident heart failure. Effect modification will be examined by smoking, obesity and comorbidities. A subgroup analysis will be done restricting sample to individuals who didn’t report or were not diagnosed with AMI prior to HF hospitalization. The reduction in hazard ratio will be evaluated after adjustment for pro-inflammatory and pro-coagulability markers (intermediaries) in a model adjusted for potential confounders (age, gender, height etc.)

PHA will be examined for the main exposure and all covariates with log – log curves and time interaction terms (Cox test). Linearity of log (HR) will be examined.

**Variables requested:**

**Visit 1:** Lung function test (FVC, FEV1), demographics (age, gender, race, center), Socio economic indicators (education and income), anthropometric measures (height, BMI, waist circumference, waist-hip ratio), comorbidities and CVD risk factors (CAD, COAD, CHF, T2DM, hypertension, LDL-cholesterol, HDL cholesterol), inflammatory and hemostatic markers (albumin, fibrinogen), von Willebrand factor (vWF), fibrinogen, D-dimer, factor VII, factor VIII, PAI-1, tPA, beta-thromboglobulin (beta-TG), CRP, and WBC count). Smoking?

**Visit 2:** Lung function test (FVC, FEV1), MIP

**Follow up through 2004:** incident CAD, incident hospitalized HF

7.a. Will the data be used for non-CVD analysis in this manuscript? **No**

7.b. **NA**

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

8.b. **NA**
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. No overlaps

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)?

**Proposals looking at risk factors of HF:**
- MP#922 Alcohol consumption and risk of congestive heart failure
- MP#927 Heart Failure Incidence and Survival: 13 Year Follow up of the ARIC Cohort
- MP#1118 Kidney Function as a Risk Factor for Incident Heart Failure
- MP#1125 Diabetes, obesity and insulin resistance as risk factors for incident hospitalized HF
- MP#1144 The Obesity Paradox in Heart Failure.
- MP#1160 Life Course Socioeconomic Exposures and Heart Failure.
- MP#1164 Hemoglobin A1c as a Risk Factor for HF Hospitalization among Persons with Diabetes.
- MP#1197 Albuminuria as a Predictor of Incident Heart Failure Hospitalization and Mortality. MP#1232 ECG Abnormalities Preceding Heart Failure: Estimation and Prediction
- MP#1276 Exhaustion and risk for congestive heart failure.

**Other Proposals with HF as focus:**
- MP#855 Retinal Microvascular Abnormalities and Congestive Heart Failure
- MP#617 Evaluation of ICD Codes to Identify Hospitalized MI Patients with Acute Congestive HF.
- MP#890B Plasma Fatty Acid Composition and Incidence of Heart Failure in Middle Aged Adults
- MP#1049 Prevalence and Prognosis of ALVSD in African Americans
- MP#1282 Outpatient Surveillance of Heart Failure.
- MP#1325 Neighborhood and Individual Socioeconomic Status and Heart Failure Rehospitalization
- MP#1325 Socioeconomic, demographic and clinical predictors of heart failure care.

**Other proposals with lung function as focus:**
- MP#56 Lung function and ultrasound (M)
- MP#551 Race and gender differences in the effects of smoking on lung function: a meta-analysis
- MP#849 Low lung infraction and incident lung cancer
- MP#850 Low lung function, lung function decline, and outcomes
- MP#851 The metabolic syndrome and low lung function
- MP#1080 Lung function, asthma, and coronary heart disease (CHD) severity
- MP#1091 Impaired Lung Function Associated with Polymorphisms in Beta-Adrenergic Receptors (ADRB) and Endothelin Receptors (EDNR)
- MP#1220 Relationship of Lung Function with ARMD and Retinal Vascular Disease
- MP#1239 Matrix Metalloproteinase Polymorphisms Associated with Impaired LF and COPD
- MP#1311 Serum uric acid, lung function and chronic obstructive pulmonary disease in adults
- MP#1356 Dietary Dairy Intake, Lung Function, and Chronic Obstructive Pulmonary Disease (COPD)

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? No

11.b. If yes, is the proposal NA

12. Manuscript preparation is expected to be completed in one to three years. The authors are aware of this fact.
References:


