ARIC Manuscript Proposal # 1674

PC Reviewed: 8/10/10	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Lung function, COPD, and the incidence of atrial fibrillation: the ARIC study

b. Abbreviated Title (Length 26 characters):
Lung function, COPD, and AF

2. Writing Group:
(Alphabetically) Agarwal SK, Alonso A, Blecker S, Chamberlain A, Enright, P, , Heiss G, Loehr L, Mc Neill AM, Punjabi N, Soliman EZ; others welcome

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

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3. Timeline:
Analysis: 3 months
First draft of manuscript: 6 months

4. Rationale:

Atrial Fibrillation (AF), a common arrhythmia, is associated with higher rates of stroke, dementia, heart failure, and mortality [1]. Little is known about risk factors of AF among minorities including African Americans as most available studies have examined whites [1].

Despite several patho-physiologic pathways and clinical observations pointing to possibly higher rates of AF among those with low lung function or airway obstruction the published literature is inconsistent. An independent association between FEV1 and AF was not seen in reports from the original Framingham cohort [2] nor from the Renfrew/Paisley Study[3]. In contrast, reports from the Cardiovascular Health Study [4] and the Copenhagen City Heart Study[5] found such associations. Most of these studies had limited power to examine heterogeneity by smoking status (in particular among non smokers) or to examine possible difference by race [4]. Surprisingly, few reports suggest that patients with Chronic Obstructive Pulmonary Disease (COPD) have higher incidence rates of AF hospitalization [6-7]. Moreover, there are no reports on an association between COPD (as verified by spirometry) and AF.

AF could be a mediator of the strong relationship between lower lung function and stroke seen in several studies, including ARIC [8]. In the ARIC cohort, no association was observed between lung function and stroke among blacks (who reportedly have lower incidence of occurrence AF). Perhaps the association of lung function with AF varies by race.

Considering putative biological mechanisms, mild pulmonary hypertension commonly accompanies the pathology associated with COPD (alveolar destruction, hypoxia, and intimal proliferation)[9]. CT-defined emphysema and airflow obstruction were reported to be linearly associated with diastolic dysfunction [10], a precursor of increased atrial pressure. Fibrosis of pulmonary veins[11] or stretching of pulmonary veins via increased intra-atrial pressure[12] may also play a role. A role of pulmonary veins in the initiation and maintenance of AF among many individuals is well accepted[13-14]. Higher levels of circulating inflammatory markers as well as localized inflammation in the atria have been shown to be association with AF [15]. Considering that higher systemic levels of inflammatory or procoagulability markers are seen in individuals with low lung volume too, these may be potential confounders or mediators.

We observed a strong association between lower FVC, COPD and incidence of heart failure (HF) in the ARIC study (manuscript #1378). Cross sectional data similarly showed a higher prevalence of AF in patients with severe HF (NYHA Class I $< 5\%$ and up to 50% in Class IV CHF patients)[16]. It is well known that HF and AF share several common risk factors. Also, HF is a strong predictor of AF by modifying atrial substrate and possibly increasing of both initiation and maintenance of AF by modifying neuro-humoral milieu. Thus, establishing whether an association exists between lung function and COPD with AF after adjusting for incident HF should be informative. Low FVC is also associated with incident diabetes[17-18], left ventricular hypertrophy[19], sub-clinical atherosclerosis (measured by ankle-brachial index and intima-media

thickness)[20], and incident ischemic cardiac disease [19, 21-24]. Thus, examination of putative association after adjustment of incident CHD would suggest involvement of pathways beyond coronary atherosclerosis.

The goals of this proposal are to assess the relationship between airway obstruction, low FVC, and incident AF. Since a differential relationship may exist by race, the ARIC cohort provides an opportunity to explore the lower risk of AF seen in African Americans. Also, smoking habits and socio-economic status (confounded by race in ARIC) will be considered in examining a relationship between lung function and AF. This relationship may differ by co-morbidities and may 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 disease and AF relationship and perhaps suggest preventive strategies.

5. Main Hypothesis/Study Questions:

We hypothesize that poor lung function at study baseline in individuals without AF is associated with increased risk of subsequent AF; that this relationship exists among never smoker and independent of incident CAD or HF, and that it will be attenuated by adjustment for pro-inflammatory, pro-coagulability markers.

We propose to investigate the following questions with special attention to interactions by race (whenever possible) and gender. Race and gender specific quartiles of lung volumes will be used to examine the associations.

1. Estimate the association of COPD (self reported and GOLD classification) at study baseline with risk of incident AF.

    i. The above relation is confounded by smoking, obesity and baseline comorbidity (CAD and Diabetes), and socio-economic status.

2. Estimate the association of lung function (FVC, FEV1, and FEV1/FVC, after appropriate adjustments for gender and height) with risk of incident hospitalized AF.

    i. The above relation is confounded by smoking, obesity and baseline comorbidity (CAD and T2DM), and socio economic status

3. Assess whether the above relationship exists in the subset of the cohort without CAD or HF prior to incident AF.

    i. Adjustment for systemic markers of inflammation, hypercoagulability, maximal inspiratory pressure (MIP) attenuate the above relationship.

4. Those with greater decline in FVC (between visit 1 and visit 2) are at higher risk of incident hospitalized AF after adjusting for baseline FVC (visit 1).

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 methodological limitations or challenges if present).

Study Design

ARIC cohort data with events through 2007 will be used. Lung function measures and respiratory illness diagnosis will be derived from exam visits 1 and 2. Time to event will be defined by time from study baseline through earliest of new-onset AF, or loss to follow up, or 31st December 2007.

Main independent variable

We propose to use measured FEV1 rather than % predicted FEV1 but will also explore if relationship changes if % predicted FEV1 is used instead. Also, COPD defined using various ways a). self reported physician diagnosis, b) chronic cough and sputum production over ≥ 3 months in 2 contiguous years, c) using FEV1/FEV ratio during visit 1 and visit 2 will be used.

Outcome

The ascertainment of incident AF in ARIC has been previously described.[25-26] Briefly, AF was determined from three sources: ECGs done at baseline and follow-up visits, discharge codes from hospitalizations and death certificates. Most AF cases in ARIC were identified from discharge hospitalizations. A validation study in ARIC determined that the sensitivity of discharge codes for AF was ≥ 84% and the positive predictive value ≥ 89%.[25]

Inclusion and exclusion criteria

From the complete ARIC cohort (n = 15,792), we will exclude the following participants from our analyses: poor quality spirometry, no baseline ECG, poor quality ECG recordings (QC grade 5), ECG-defined prevalent AF at baseline, missing main covariates, reported race other than black or white.

Statistical analysis

Cox proportional hazards regression models will be used to assess the relationship between lung disease (self reported and modified GOLD classification) and incident AF. Racial and gender differences will be explored in subgroup analysis. Also, effect modification will be examined for smoking and other comorbidity. At study baseline 54% of the women and 30% of the men were never smokers, thus providing adequate statistical power to examine the association in this subgroup to effective avoid residual confounding by active smoking.

Similarly, Cox regression models will be used to examine the relationship between functional measures FVC, FEV1 (divided by quartiles) and incident AF. Effect modification will be examined by smoking, prevalent CHD status. Analysis with adjustment for incident CHD and incident HF as time varying covariates will be done. The reduction in hazard ratio will be evaluated after adjustment for pro-inflammatory and

pro-coagulability markers (intermediaries) [specify] in a model adjusted for potential confounders (age, gender, height etc.)

Proportionality of hazards 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. Also, dose response relationship will be examined using restricted cubic splines.

Variables requested:

Visit 1: Lung function test (FVC, FEV1), demographics (age, gender, race, center), Socio economic indicators (education and income), anthropometric measures (height, BMI), comorbidites and CVD risk factors (CAD, CHF, T2DM, hypertension, LDL-cholesterol, HDL cholesterol), inflammatory and hemostatic markers (albumin, fibrinogen), von Willebrand factor (vWF), fibrinogen, smoking status, and cigarette years of smoking

Visit 2: Lung function test (FVC, FEV1)

Follow up through 2007: incident CAD, incident HF, incident AF

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

8.a. Will the DNA data be used in this manuscript? 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

No overlap found

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)?

MS # 1351: Incidence of atrial fibrillation in a bi-racial cohort: the ARIC study
MS # 1377: Relationship between pulmonary disease, lung function and incident hospitalized heart failure: The ARIC study

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* 2008.09, 2008.12)

___ 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/

12. 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.

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4. Psaty, B.M., et al., *Incidence of and risk factors for atrial fibrillation in older adults.* Circulation, 1997. **96**(7): p. 2455-61.
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6. Mapel, D.W., D. Dedrick, and K. Davis, *Trends and cardiovascular co-morbidities of COPD patients in the Veterans Administration Medical System, 1991-1999.* COPD, 2005. **2**(1): p. 35-41.
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9. McLaughlin, V.V., et al., *ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association.* Circulation, 2009. **119**(16): p. 2250-94.
10. Barr, R.G., et al., *Percent emphysema, airflow obstruction, and impaired left ventricular filling.* N Engl J Med, 2010. **362**(3): p. 217-27.
11. Everett, T.H.t. and J.E. Olgin, *Atrial fibrosis and the mechanisms of atrial fibrillation.* Heart Rhythm, 2007. **4**(3 Suppl): p. S24-7.
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14. Pappone, C., et al., *Circumferential radiofrequency ablation of pulmonary vein ostia: a new anatomic approach for curing atrial fibrillation.* Circulation, 2000. **102**(21): p. 2619.

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16. Maisel, W.H. and L.W. Stevenson, *Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy.* Am J Cardiol, 2003. **91**(6A): p. 2D-8D.
17. Engstrom, G. and L. Janzon, *Risk of developing diabetes is inversely related to lung function: a population-based cohort study.* Diabet Med, 2002. **19**(2): p. 167-70.
18. Yeh, H.C., et al., *Vital capacity as a predictor of incident type 2 diabetes: the Atherosclerosis Risk in Communities study.* Diabetes Care, 2005. **28**(6): p. 1472-9.
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24. Schroeder, E.B., et al., *Lung function and incident coronary heart disease: the Atherosclerosis Risk in Communities Study.* Am J Epidemiol, 2003. **158**(12): p. 1171-81.
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