ARIC Manuscript Proposal #2219

PC Reviewed: 9/10/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Pathophysiologic characterization of dyspnea in the elderly: The ARIC study

b. Abbreviated Title (Length 26 characters):
Characterization of Dyspnea in ARIC

2. Writing Group:
Writing group members: Amil M Shah, Brian Claggett, Hicham Skali, Dalane Kitzman, Kunihiro Matsushita, Laura Loehr, Scott D. Solomon; Others welcome.

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

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3. Timeline:
Analysis will begin once this manuscript proposal is approved. Anticipate initial manuscript completion in approximately 6 months following proposal approval with final manuscript completion once Visit 5 is complete (3/2014).

4. Rationale:

Chronic dyspnea occurs in approximately 10%,[1,2] and is particularly common among the elderly, with at least moderately severe dyspnea reported in approximately 25% of persons >65 years of age.[3,4,5] Participant-reported dyspnea is also associated with a higher risk of mortality,[6] the majority of which appear to be cardiovascular in origin.[4] Indeed, participant reported dyspnea appears to be a more powerful predictor of clinical outcomes than objective physiologic measures such as pulmonary function/spirometry.[7] Among the elderly, dyspnea is also associated with worse functional capacity and a higher prevalence of anxiety and depression.[5]

Although common, the determining the etiology of dyspnea, particularly in the elderly, is challenging. Cardiovascular, pulmonary, hematologic, renal, and musculoskeletal dysfunction may all contribute.[8] Cardiovascular causes include left ventricular systolic and diastolic function, excessive arterial stiffness and associated blood pressure lability, chronotropic incompetence, and valvular disease. Pulmonary causes include obstructive and restrictive lung disease and pulmonary vascular disease including pulmonary hypertension. Additional causes include significant anemia, altered fluid handling related to co-existing renal impairment, and deconditioning. Significant differences exist between elderly men and women in both the prevalence and prognostic implications of dyspnea although the mechanisms responsible for this gender difference remain unclear.[2,4] Furthermore, little is known regarding differences in the prevalence and underlying physiologic impairments responsible for dyspnea by race/ethnicity.

A better understanding of the physiologic perturbations characterizing elderly individuals with dyspnea, and distinguishing them form their asymptomatic peers matched on key demographic characteristics (age, gender, race/ethnicity), will provide novel insight into the relative contributions of multiple organ systems to dyspnea in the elderly. Detailed phenotyping of cohort participants in ARIC Visit 5 offers the unique opportunity to identify cardiac and non-cardiac organ dysfunction characterizing dyspnea in the elderly. In addition, this large biracial cohort is uniquely positioned to investigate gender and race/ethnicity-based differences in these relationships.

5. Main Hypothesis/Study Questions:

We hypothesize that, compared to the elderly without significant dyspnea, elderly persons with dyspnea will demonstrate worse function of multiple organ systems including cardiovascular, pulmonary, renal, and hematopoetic.

Specifically, we aim to:

1. Define the prevalence and clinical correlates of any dyspnea and dyspnea of at least moderate severity in the study cohort overall, and stratified by gender and race/ethnicity.
2. Characterize cardiac and non-cardiac organ dysfunction among participants reporting dyspnea, and determine whether these metrics differ compared to participants not reporting dyspnea overall and to non-dyspneic participants matched for age, gender, and race/ethnicity. The following measures will be evaluated (see analysis section below for further details): (1) LV structure and systolic function; (2) LV diastolic function; (4) biomarkers of myocardial stress

and injury; (5) pulmonary pressure, vascular resistance, and right ventricular function; (6) arterial stiffness; (7) renal function; (8) pulmonary function; (9) hematologic function/anemia; (10) dysglycemia; and (11) anthropometrics.

3. In a cross-sectional fashion, estimate the population attributable risk for dyspnea associated with dysfunction in each of these domains in the Visit 5 population overall, and by gender and race/ethnicity.

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:

This will be a cross-sectional analysis based on data collected at ARIC Visit 5.

Inclusion/exclusion criteria:

Inclusion criteria for the analysis include: (1) dyspnea scale, echocardiographic, vascular stiffness, spirometry, renal function, and hematologic data at Visit 5.

Key variables of interest:

1. Dyspnea scale (visit 5): Based on Respiratory Questionnaire items 5-10.
2. Anthropometrics (visit 5): height, weight, BMI, BSA, waist:hip ratio
3. Echocardiographic variables (visit 5 echo): (1) LV structure (LV end-diastolic and end-systolic volumes and dimensions), wall thickness, relative wall thickness, and mass); (2) LV diastolic function (E wave, A wave, E wave deceleration time, TDI E', and LAVi); (3) LV systolic function (LVEF, mid-wall fractional shortening, longitudinal strain, circumferential strain); (4) pulmonary hemodynamics (estimated PASP based on TR jet velocity, PVR) and right ventricular function (RVFAC, TDI tricuspid annular S')
4. Cardiac biomarkers of stress and injury (visit 5): NT-proBNP, hs-TnT
5. Vascular function variables (visit 5): systolic blood pressure, diastolic blood pressure, mean arterial pressure, pulse pressure, carotid-femoral pulse wave velocity, forward wave amplitude, ABI
6. Pulmonary function variables (visit 5): FEV_1, FVC, FEV_1/FVC ratio
7. Renal function variables (visit 5): eGFR based on serum creatinine and/or cystatin C, urine albumin:creatinine ratio
8. Hematologic variables (visit 5): hemoglobin and hematocrit
9. Measures of dysglycemia (visit 5): hemoglobin A1C, fasting glucose
10. Measures of physical functioning (visit 5)
11. Clinical covariates (visit 5): age, gender, race/ethnicity, heart rate, history of hypertension, diabetes, dyslipidemia, coronary artery disease, prior MI or revascularization procedure, prior stroke or TIA, peripheral arterial disease, heart failure, prior hospitalization for heart failure

Data analysis:

The prevalence and severity of dyspnea will be defined based on items 5 – 10 of the Respiratory Questionnaire, which is an approximation of the MRC breathlessness scale.[9] This is a 5 level scale, with the participant score based on the question that best described the participants level of activity. This scale has been widely applied[1,2,3,4,5,6] and has demonstrated prognostic relevance in COPD and coronary artery disease.[3] For the primary analysis, dyspnea will be defined dichotomously (yes/no) based on a MRC score of ≥2 (breathlessness related to exercise intolerance or at rest). In a secondary analysis, we will define three groups: no dyspnea (MRC score 1), dysnea with exertional limitation (MRC score 2-3), and severe dyspnea (MRC score ≥4). Participants reporting dyspnea will be compared to all cohort participants not reporting dyspnea. In a sensitivity analysis, we will compare participants reporting dyspnea to cohort participants not reporting dyspnea who are age, gender, and race/ethnicity matched.

Basic descriptive statistics will be performed in the population stratified by presence of dyspnea or not. Between-group comparisons will be performed using a Fisher's exact test for categorical variables, t-test for normally distributed continuous variables, and Wilcoxon rank sum test for non-normally distributed continuous variables. Multivariable adjustment will be performed using linear regression (continuous outcome variables) and logistic regression (categorical outcome variables) as appropriate, adjusting first for age, gender, and race/ethnicity, then additionally by clinical variables that differ significantly between the two groups. Additional sensitivity analysis will be performed restricting the above comparison to persons reporting dyspnea compared to age, gender, and race/ethnicity matched individuals not reporting dyspnea. Both univariate and multivariable analysis will be performed as described above.

To quantify the relative contribution of dysfunction in various organ systems to dyspnea in the elderly, the population attributable risk (PAR) associated with dysfunction of each organ will be calculated. The presence of dyspnea will be the primary response variable. The following domains of organ dysfunction will act as the predictor variables: LV systolic function, LV diastolic function, LV remodeling, pulmonary vascular and RV dysfunction, pulmonary dysfunction, systemic arterial dysfunction, renal dysfunction, anemia, and dysglycemia. Predictor variables will be dichotomized for this analysis, creating indicators of absence or presence of dysfunction. Multiple measures can characterize a given domain of organ dysfunction. To identify the optimal measure to represent each domain, for each domain of organ dysfunction we will employ multivariable logistic regression models with dyspnea status as the outcome and all candidate measures as predictors and will select the measure with the highest chi-square value. For continuous variables, where no *a priori* definition of abnormal exists, dysfunction will be defined as the most abnormal quartile. For each domain of organ dysfunction, the following candidate measures (listed in parentheses) will be considered: LV systolic function (LVEF, mid-wall fractional shortening, TDI S', longitudinal strain, circumferential strain), LV diastolic function (LAVi, E', E/E', E/A ratio, deceleration time), LV remodeling (LV end-diastolic volume, LV mass index, RWT), pulmonary vascular and right ventricular dysfunction (peak TR velocity, pulmonary vascular resistance, RV fractional area change, TDI tricuspid annular S'), pulmonary dysfunction (FEV1, FCV, FEV1/FVC ratio), arterial dysfunction (SBP, DBP, MAP, pulse pressure, pulse wave velocity), renal dysfunction (eGFR, proteinuria), anemia (hemoglobin,

hematocrit), dysglycemia (diabetes, fasting glucose, HbA1c), and obesity (BMI, BSA, waist:hip ratio).

As there are multiple methods to calculate PAR %,[10] we will use a method that is considered internally valid when adjusted relative risks must be used to account for possible confounding: PAR % = pd_i *[(RR_i-1)/RR_i], where pd_i is the proportion of total cases in the population arising from the *i*th exposure category and RR_i is the adjusted relative risk for the *i*th exposure category. The PAR associated with each domain of organ dysfunction listed above will be estimated in the overall population using the OR estimates derived from multivariable models adjusting for all selected organ dysfunction indicators, in addition to age, sex, race, and site. Gender- and race/ethnicity-specific estimates will then be obtained by applied the same models to subgroups of the ARIC population (i.e., males, females, blacks, whites).

Anticipated methodologic limitations:

A major limitation for this analysis is its cross-sectional design. Ideally, we would be able to relate cardiac and non-cardiac measures characterizing dyspnea with the risk of death or HF hospitalization among persons with dyspnea. However, this data will not be available for several years and future manuscript proposals will focus on this analysis.

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

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ____ Yes ____ No
(This file ICTDER03 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 file ICTDER03 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/search.php

___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)?

#1516: Saul Blecker, Stuart Russell, Pete Miller, Herman A. Taylor, Ervin Fox, Fred Brancati, Joe Coresh. Left ventricular dysfunction and risk of hospitalization for dyspnea due to noncardiac causes.

#1891: Deepak K. Gupta, Davide Castagno, Madoka Takeuchi, Amil M. Shah, Scott D. Solomon; Ervin Fox; Ken Butler; Tom Mosley. Phenotypic profile of heart failure with preserved ejection fraction in African Americans: risk factors, cardiac structure and function, and prognosis.

#2061: Umair Khalid, Anita Deswal, Biykem Bozkurt, Salim Virani, Vijay Nambi, Christie Ballantyne, Patty Chang, Laura Loehr, Wayne Rosamond, Sunil Agarwal. BNP as a prognostic marker in obese patients with acute decompensated heart failure and preserved ejection fraction.

#1942: Deepak K. Gupta, Amil M. Shah, Scott D. Solomon; Others welcome. Cardiac structure and function in elderly African-Americans with heart failure with preserved ejection fraction.

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 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.

References

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[9] Stenton C. The MRC breathlessness scale. *Occup Med (Lond)* 2008;58:226-7.

[10] Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health* 1998;88:15-19.