ARIC Manuscript Proposal #2117

PC Reviewed: 4/9/13 Status: A Priority: 2
SC Reviewed: _________ Status: _____ Priority: ____

1.a. Full Title: Relationship between pulmonary airflow obstruction, cardiac structure and function, and heart failure risk in a biracial elderly cohort: The ARIC study

b. Abbreviated Title (Length 26 characters):
Cardiopulmonary interactions in ARIC

2. Writing Group:

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]

First author: Amil M Shah, MD MPH
Address: 75 Francis Street
          Boston, MA 02115
          Phone: 617-525-6733          Fax: 617-582-6027
          E-mail: ashah11@rics.bwh.harvard.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: Scott D Solomon, MD
Address: 75 Francis Street
          Boston, MA 02115
          Phone: 857-307-1960          Fax: 857-307-1944
          E-mail: ssolomon@rics.bwh.harvard.edu

3. Timeline:
Analysis will begin once this manuscript proposal is approved. Anticipate initial manuscript completion in approximately 3 months following proposal approval with final manuscript completion once Visit 5 is complete (9/2013).

4. Rationale:
Heart failure (HF) is a critical public health concern, afflicting 5 million Americans\(^1\) and disproportionately burdening the elderly, with over 80% of HF hospitalizations occurring in persons over 65 years of age. Of particular concern amongst the elderly, HF with preserved ejection fraction (HFrEF) accounts for 50% of HF cases,\(^2,3\) is increasing in prevalence, and causes substantial morbidity,\(^4,5\) mortality,\(^6,7\) and resource utilization. While LV diastolic dysfunction is thought to be a central cardiac perturbation underlying this heterogeneous syndrome,\(^8\) non-cardiac co-morbidities are also highly prevalent.\(^9\) The cardiovascular and pulmonary systems work in concert to supply oxygenated blood to the body and ensure adequate tissue perfusion, and disorders affecting either can manifest as dyspnea. Numerous studies have established an association between pulmonary airflow limitation (obstructive disease) and risk of incident HF.\(^10,11,12\) Airflow obstruction is association with an increased risk of incident HFpEF in particular.\(^9\)

Significant elevation in pulmonary vascular resistance (PVR), as seen in pulmonary arterial hypertension (PAH), leads to right ventricular (RV) hypertrophy and enlargement, flattening of the interventricular septum, and reduced RV stroke volume.\(^13\) Together, these result in impaired left ventricular (LV) filling and diastolic dysfunction – indeed, in PAH reduction in PVR is associated with coupled improvement in RV function and indices of LV diastolic function.\(^14\) These pathophysiologic derangements are also well described in severe obstructive lung disease (COPD), where advanced parenchymal disease can lead to pulmonary vascular obliteration and elevated PVR.\(^15\) Both the degree of airflow obstruction and elevation in pulmonary arterial pressure are significant predictors of survival in COPD,\(^16\) and severe COPD is associated with smaller LV diastolic volume, reduced LV diastolic filling, and septal flattening.\(^15\) Recent data from the MESA cohort has demonstrated an association between much milder degrees of airflow obstruction and reduced LV diastolic volume and stroke volume.\(^17\) In addition, limited data from small studies (n=15) suggest that impaired LV diastolic filling is also observed in COPD in the absence of pulmonary hypertension.\(^18\) These findings question whether the pathophysiologic mechanisms involved in LV compromise in severe emphysema also occur with less severe degrees of airway obstruction, and suggest alternative mechanisms may be at play. Recent studies suggest that airflow obstruction may influence not only the pulmonary vascular circuit but may also primarily effect preload and afterload. At least one small study (n=13) suggests that elevated intrathoracic pressure associated with severe pulmonary hyperinflation may be associated with reduced intrathoracic blood volumes, with reduced LV and RV size.\(^19\) Additional findings from MESA suggest that, even in the absence of severe obstruction, the degree of pulmonary hyperinflation is an important predictor of LV mass.\(^20\) The magnitude of this association was similar to that of hypertension, suggesting a potentially significant effect of pulmonary hyperinflation on intrathoracic pressure and therefore LV afterload. However, a major limitation of studies to date has been the absence of an integrated assessment of RV function, the pulmonary vascular circuit (PVR, PASP), and LV systolic and diastolic function.

Critical gaps in our knowledge of cardiopulmonary interactions in persons without severe COPD include: (1) The relationship between lesser degrees of airflow obstruction and PVR and RV function; (2) The relationship between airflow obstruction and LV relaxation (as opposed to filling) dynamics and LV deformation (longitudinal and
circumferential strain) despite normal LVEF; (3) The magnitude of association of echo measures of ventricular function and pulmonary hemodynamics compared to measures of airflow obstruction, with NT-proBNP, a soluble risk marker for HF; (4) Whether these cardiopulmonary relationships vary by gender, race/ethnicity, or prior smoking status. Comprehensive echocardiography and spirometry for ARIC Visit 5 provides a unique opportunity to explore these cardiopulmonary interactions.

5. Main Hypothesis/Study Questions:

We hypothesize that, among ARIC participants without prevalent cardiovascular disease and with LVEF>50%, lower FEV₁/FVC will be associated with: (1) smaller LV size, increased LV wall thickness, higher PVR and PASP, worse RV function, reduced LV diastolic relaxation (TDI E’) and early filling (E wave velocity); and (2) serum NT-proBNP independent of LV structure and function but not after adjustment for PVR and RV function. We further hypothesize that these associations will be more pronounced in smokers compared to non-smokers, but otherwise uniform between genders and race/ethnicity.

Specifically, we aim to:
1. Determine the association of FEV₁/FVC ratio with measures of (1) LV structure (LVEDV, LVESV, wall thickness, mass, relative wall thickness), (2) LV systolic function (LVEF, stroke volume, mid-wall fractional shortening, longitudinal strain, circumferential strain), (3) LV diastolic function (E wave velocity, E/A ratio, TDI E’, LAVi), (4) pulmonary hemodynamics (PVR, PASP), and (5) RV function (RVFAC, TDI tricuspid annular S’).
2. Determine the relationship of FEV₁/FVC with serum NT-proBNP levels in additive multivariable models progressively adjusting for: (1) demographics and anthropometrics, (2) LV structure and function, (3) pulmonary hemodynamics, and (4) RV function.
3. Evaluate whether the relationship between FEV₁/FVC ratio and cardiac structure and function is significantly modified by (1) gender, (2) race/ethnicity, and (3) smoking status.

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) echocardiographic data at Visit 5 with a reading center determined LVEF≥50%; (2) spirometry data at Visit 5 of adequate quality.
(quality grade A, B, or C based on variables QFEV1 and QFVC); (3) absence of prevalent cardiovascular disease at Visit 5, defined as history of CHD, HF, stroke, PAD, or atrial fibrillation.

**Key variables of interest:**

1. Echocardiographic variables (visit 5 echo) of LV structure (LV end-diastolic and end-systolic volumes and dimensions), wall thickness, relative wall thickness, and mass), LV diastolic function (E wave, A wave, E wave deceleration time, TDI E’, and LAVi), LV systolic function (LVEF, mid-wall fractional shortening, longitudinal strain, circumferential strain), pulmonary hemodynamics (estimated PASP based on TR jet velocity, PVR), and right ventricular function (RVFAC, TDI tricuspid annular S’)

2. Pulmonary function variables (isit 5): FEV₁, FVC, predicted FEV₁, predicted FVC, spirometry quality indicator (variables QFEV1, QFVC)

3. Laboratory values (visit 5): NT-proBNP, serum albumin and creatinine, urine albumin and creatinine, hemoglobin and hematocrit, glucose, hemoglobin A1C, total cholesterol, triglycerides, HDL, LDL

4. Clinical covariates (visit 5): age, gender, race/ethnicity, height, weight, blood pressure, heart rate, history of hypertension, diabetes, dyslipidemia, coronary artery disease, prior MI or revascularization procedure, prior stroke or TIA, PAD, HF, prior hospitalization for HF

**Data analysis:**

The primary predictor variable of interest will be FEV₁/FVC ratio. Secondary analyses (similar to those outlined below for FEV₁/FVC ratio) will be performed with FEV₁ and FCV individually, and also with percent predicted FEV₁ and FVC.

Participants will be classified based on quartile of FEV₁/FVC ratio. Clinical covariates, laboratory variables, and echocardiographic measures of structure and function will be described by FEV₁/FVC ratio quartile, and association assessed by trend test. Associations will be further assessed using multivariable linear regression models, adjusting for clinical covariates and certain laboratory measures (renal function markers, hematologic markers, hemoglobin A1C) which vary significantly across FEV₁/FVC ratio quartiles. The presence of non-linear associations between pulmonary measures and key measures of cardiac structure and function will be assessed using smoothed splines and polynomial terms in regression models.

To explore whether an association between FEV₁/FVC ratio and serum NT-proBNP (an established marker of HF risk) exists independent of perturbations of cardiac structure and function known to be associated with COPD, we will employed additive multivariable models adjusting for sequentially more variables. Five regression models will be constructed: Model 1 will adjust for age gender, and race/ethnicity; Model 2 will additionally adjusted for clinical covariates significantly associated with pulmonary function and NT-proBNP level; Model 3 will additionally adjust for key measures of LV structure (LVESV, wall thickness); Model 4 will additionally adjust of LV diastolic measures (TDI E’, E/E’ ratio, LAVi); and Model 5 will additional adjust for pulmonary vascular measures (PASP, PVR) and RV function (TDI tricuspid annular S’).
Finally, as prior studies have demonstrated significant effect modification of smoking status on the relationship between pulmonary function and measures of cardiac structure and function,\textsuperscript{17} we will assess for effect modification using multiplicative terms. As the cardiovascular response to hemodynamic stress also appear to vary by gender\textsuperscript{21,22} and race/ethnicity,\textsuperscript{23,24,25} we will assess for effect modification by gender and race/ethnicity on the relationship between FEV\textsubscript{1}/FVC and measures of cardiac structure and function.

\textit{Anticipated methodologic limitations:}

This study is cross-sectional in design so inferences regarding causality cannot be made. Future analyses will evaluate the independent value of FEV\textsubscript{1}/FVC measured longitudinally over ARIC visits 1 and 2 to predict cardiac structure and function at Visit 5. Full lung volumes, including total lung capacity and residual volume, would be informative as measures of hyperinflation but are not available for this analysis. Pulmonary hemodynamics (PASP, PVR) is only available in a subset of ARIC participants with adequate tricuspid regurgitation to perform these measurements. We will determine how these participants differ from those without measurable PASP and PVR to assess for systematic bias. Residual confounding of the relationship between pulmonary function and cardiac structure and function by common co-morbidities cannot be fully addressed by multivariable modeling. Sensitivity analyses will be performed among participants without established cardiovascular risk factors (hypertension, diabetes, chronic kidney disease, obesity).

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\textunderscore{OTH} = “CVD Research” for non-DNA analysis, and for DNA analysis RES\textunderscore{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\textunderscore{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:  \url{http://www.cscn.unc.edu/ARIC/search.php}
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)?


#1811: Oluleye OW, Folsom AR, Nambi V, Ballantyne C. Association of high sensitive Troponin T (hs-cTnT), N-terminal pro-brain natriuretic peptide (NT-proBNP) and high sensitivity C-reactive protein (hs-CRP) with cause-specific mortality: ARIC study.


11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  
   ___ Yes  ___ 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/](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


14 Shah AM, Campbell P, Barst RJ, Peacock A, Quinn D, Solomon SD. Effect of imatinib as add-on therapy on cardiac structure and function in patients with significant pulmonary arterial hypertension. European Heart Fail Congress 2012 (abstract)


