ARIC Manuscript Proposal #2181

PC Reviewed: 5/14/13 Status: A Priority: 2
SC Reviewed: _________ Status: _____ Priority: ____

1.a. Full Title: Pathophysiologic characterization of pulmonary hypertension in an elderly cohort: The ARIC study

b. Abbreviated Title (Length 26 characters): Pulmonary hypertension in ARIC

2. Writing Group:
   Writing group members: Amil M Shah, Hicham Skali, 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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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).

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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:
The prevalence of pulmonary hypertension increases with age and is associated with increased mortality, even among individuals without prevalent cardiopulmonary disease.\textsuperscript{1} Pulmonary pressures are related to pulmonary vascular resistance (driven largely by small arteriolar and pre-capillary arteriole resistance), pulmonary arterial compliance (related to large vessel stiffness), and downstream left heart filling pressure with associated pulmonary venous hypertension.\textsuperscript{2,3} Abnormalities of all three of these determinants have been described with aging. Perhaps most widely appreciated, age-related changes in left ventricular diastolic function are frequently detected in asymptomatic older persons. For example, in the Olmstead County cohort, some degree of diastolic dysfunction was noted in 71\% of participants ≥75 years old, compared to 12\% of those 45-54 years old.\textsuperscript{4} Furthermore, age-related increase in pulmonary artery systolic pressure in the community is significantly related to higher LV filling pressure.\textsuperscript{1} The stiffness of the pulmonary artery also appears to increase with age, in concert with age-related alterations in the elastin and collagen content of the pulmonary arterial vessels.\textsuperscript{5,6,7} This increase in PA stiffness increases RV pulsatile load and is associated with RV dysfunction and increased mortality in pulmonary arterial hypertension.\textsuperscript{8,9} Small single center studies also suggest that PVR is higher in older individuals.\textsuperscript{10,11} However, the relative contributions of pulmonary arterial stiffness, PVR, and LV filling pressure to pulmonary hypertension in the elderly are unclear. Additionally, the clinical correlates of PA stiffness and elevated PVR in the elderly has not been evaluated in a population based cohort. Finally, the influence of gender and race/ethnicity on the pathophysiology of pulmonary hypertension in the elderly is unknown. Comprehensive echocardiography in ARIC Visit 5 provides a unique opportunity to address these critical gaps in our understanding of pulmonary vascular disease in the elderly.

5. **Main Hypothesis/Study Questions:**

We hypothesize that, among elderly community dwelling individuals, elevated Pulmonary Artery Systolic Pressure (PASP) will be associated with higher Pulmonary Vascular Resistance (PVR), greater pulmonary vascular stiffness, and higher LV filling pressure. We further hypothesize that abnormality of all four measures (PASP, PVR, stiffness, and LV filling pressure) will be associated with RV dysfunction.

Specifically, we aim to:

1. Determine the clinical and echocardiographic correlates of pulmonary vascular measures (PASP, PVR, and stiffness) in the ARIC cohort overall.
2. Determine the association of PASP with (1) PVR, (2) pulmonary vascular stiffness, and (3) LV filling pressure (E/E’ ratio, LAVi).
3. Determine the relationship between pulmonary vascular measures (PASP, PVR, and stiffness) and RV function (RV FAC, tricuspid annular S’).
4. Evaluate whether the relationships between PASP and PVR, stiffness, and LV filling pressure are significantly modified 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:**
This analysis will include all participants with echocardiographic data at Visit 5 with measurable tricuspid regurgitation jet velocity.

**Key variables of interest:**
1. Echocardiographic variables (visit 5 echo) of pulmonary hemodynamics (estimated PASP based on TR jet velocity, PVR, pulse pressure), right ventricular function (RVFAC, TDI tricuspid annular S’), LV structure (LV end-diastolic and end-systolic volumes and dimensions), wall thickness, relative wall thickness, and mass, LV filling pressure (E/E’ ratio), LV diastolic function (E wave, A wave, E wave deceleration time, TDI E’, and LAVi), and LV systolic function (LVEF, tissue Doppler S’)
2. Pulmonary function variables (Visit 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, prior VTE

**Data analysis:**
This analysis will utilize echocardiographic estimates of the following hemodynamic measures:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Calculation</th>
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<tr>
<td>PASP (mmHg)</td>
<td>4*(peak TR jet velocity)$^2$+5</td>
</tr>
<tr>
<td>PVR (Woods units)</td>
<td>0.1618 + 10.006 * (peak TR velocity/RVOT VTI)</td>
</tr>
<tr>
<td>Stiffness</td>
<td>Pulmonary artery pulse pressure (PP)/SV Where PP = PASP – PADP, and DBP = (3<em>MPAP) – (2</em>PASP) MPAP = (PVR*CO) + LAP</td>
</tr>
<tr>
<td>LA pressure (LAP; mmHg)</td>
<td>11.96 + (0.596*E/E’ ratio)</td>
</tr>
</tbody>
</table>

For specific aim 1, participants will be classified based on quartile of PASP. Clinical covariates, laboratory variables, and echocardiographic measures of structure and function will be described by PASP quartile, and association assessed by trend test. The presence of non-linear associations between PASP and key measures of cardiac function will be assessed using non-linear regression models.
structure and function will be assessed using smoothed splines and polynomial terms in regression models. Parallel analyses will be performed for PVR and stiffness.

For specific aim 2, we will determine the association of PASP with PVR, stiffness, and LV filling pressure (E/E’ ratio) using Pearson correlation for univariate analysis. We will then use multivariable linear regression with PASP as the outcome variable and PVR, stiffness, and E/E’ ratio as predictor variables to determine the relative strength of association of each measure with PASP. An additional sensitivity analysis will be performed restricting analysis to participants without prevalent cardiopulmonary disease at Visit 5, defined as history of CHD, HF, stroke, PAD, atrial fibrillation, VTE, or lung disease based on Visit 5 spirometry.

For specific aim 3, we will use Pearson correlation to assess the unadjusted relationship of PASP, PVR, stiffness, and E/E’ ratio with measures of RV function (RV FAC and TA S’). For associations that are significant in univariate analysis, we will then perform adjusted analysis using multivariable linear regression models with RV function measure (RV FAC or TA S’) as the outcome variable, the pulmonary hemodynamic measure (PASP, PVR, stiffness, or E/E’) as the primary predictor of interest, and measures associated with the pulmonary hemodynamic variable (from SA 1 above) as model covariates. Separate models will be constructed for RV FAC and TA S’ as outcomes measures, and for PASP, PVR, stiffness, and E/E’ as primary predictors.

Finally, for specific aim 4, as the cardiovascular response to hemodynamic stress also appear to vary by gender and race/ethnicity, we will assess for effect modification by gender and race/ethnicity on the relationship between PASP and PVR, stiffness, and E/E’.

Anticipated methodologic limitations:

This study is cross-sectional in design so inferences regarding causality cannot be made. Pulmonary hemodynamics (PASP, PVR, stiffness) 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. Hemodynamic measures (PASP, PVR, stiffness, LV filling pressure) are echocardiographic estimates of true hemodynamic measures, which may decrease the power of this analysis to detect significant associations. However, these measures are validated and have been previously used in clinical and epidemiologic studies. Residual confounding of the relationship between pulmonary hypertension, component pulmonary vascular measures (PVR, stiffness, E/E’), and RV dysfunction by common cardiopulmonary co-morbidities cannot be fully addressed by multivariable modeling. Sensitivity analyses will be performed among participants without established cardiovascular or pulmonary disease.

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.cscu.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)?

#633: Burchfiel CM et al. Pulmonary function and echocardiographic characteristics in African Americans.

#1867: Querejeta-Roca G et al. The association between obstructive sleep apnea, biomarkers of myocardial stress and of inflammation, and cardiovascular outcomes in the Atherosclerosis Risk in Communities study.

#2117: Shah AM et al. Relationship between pulmonary airflow obstruction, cardiac structure and function, and heart failure risk in a biracial elderly cohort: The ARIC study.

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.cscu.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


17 Kizer JR, Arnett DK, Bella JN, Paranicas M, Rao DC, Province MA, Oberman A, Kitzman DW, Hopkins PN, Liu JE, Devereux. Differences in left ventricular structure
between black and white hypertensive adults: the Hypertension Genetic Epidemiology Network study. *Hypertension* 2004;43;1182-8.