ARIC Manuscript Proposal # 3314

PC Reviewed: 12/11/18  Status: _____  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title:
Impact of left ventricular diastolic function on association between systemic arterial stiffening and elevated pulmonary pressure

b. Abbreviated Title (Length 26 characters):
Association of systemic and arterial dysfunction

2. Writing Group:
Writing group members: Kanako Teramoto, Amil Shah, Susan Cheng, Brian Claggett, Scott Solomon, Gerardo Heiss, Hirofumi Tanaka, Michelle Meyer, Kunihiro Matsushita, OTHERS

WELCOME

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ___ [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 following proposal approval with the aim of completing analysis and a manuscript within _3_ months.
4. **Rationale:**
Systemic blood pressure, systemic central arterial stiffness, and pulmonary pressure are each known to increase with age. Furthermore, population-based studies have demonstrated a positive correlation between systolic arterial pressure and pulmonary artery pressure.\(^1\) Preliminary studies suggest that age-associated pulmonary vascular remodeling and stiffening contributes to the increase in pulmonary pressure with age,\(^2\) \(^3\) \(^4\) \(^5\) \(^6\) \(^7\) \(^8\) and may be coupled with concomitant alterations in systemic central arterial stiffness. The pulmonary vasculature is directly affected by LV filling pressure and diastolic dysfunction. However, age-associated impairments in left ventricular (LV) diastolic dysfunction are well recognized,\(^9\) \(^10\) \(^11\) and may be potentiated by systemic hypertension.\(^12\) \(^13\) There is limited data regarding the extent to which the observed association between systemic and pulmonary artery pressures is mediated through left heart dysfunction (e.g. LV diastolic dysfunction and elevation in LV filling pressure). Persistence of a relationship between systemic and pulmonary arterial properties in analyses accounting for concomitant measures of left heart function would suggest shared mechanisms impacting function of both arterial beds concomitantly.

Our objective is to determine the association of systemic central arterial stiffness and hemodynamics with pulmonary artery hemodynamics after accounting for measures of left heart structure and function. We will perform a cross-sectional analysis of data acquired at ARIC Visit 5. Carotid-femoral pulse wave velocity (cfPWV), an established measures of central arterial stiffness,\(^14\) will be related to echocardiography-based measures of pulmonary vascular hemodynamics including mean pulmonary pressure, pulmonary artery systolic pressure, pulmonary artery compliance, and pulmonary vascular resistance. Potential mediators will include echocardiographic measures of LV structure, systolic and diastolic function, and filling pressure.

5. **Main Hypothesis/Study Questions:**
We hypothesize that systemic central arterial stiffening relates to higher pulmonary artery pressure, lower pulmonary arterial compliance, and higher pulmonary vascular resistance in analyses accounting for measures of LV structure and function.

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 of ARIC participants at Visit 5.

**Inclusion/exclusion criteria:**
The study sample will include participants from ARIC Visit 5 who underwent both the tonometry and echocardiography during this visit. Those with previous history of coronary artery disease, significant valvular heart disease, chronic pulmonary obstructive disease, and those with missing data for the primary exposure and outcome measures will be excluded from analyses.
Additionally, participants with BMI ≥ 40 kg/m² at Visit 5, major arrhythmias (Minnesota code 8-1-3, 8-3-1, and 8-3-2 from Visit 5 ECG), Minnesota code 8-1-2 from Visit 5 ECG with low quality PWV waveforms, aortic aneurysms/abdominal aorta diameter ≥5 cm by ultrasound at Visit 5, and self-reported history of aortic revascularization or aortic graft at Visit 5 will be excluded from our analysis with respect to the quality of PWV measurement.

**Key variables of interest:**

**Dependent variables**

Our primary dependent variables will be the measures of pulmonary pressure and right ventricular function measured by echocardiography. They include, pulmonary arterial systolic pressure (PASP) calculated based on tricuspid regurgitation (TR) peak velocity, pulmonary vascular resistance (PVR) calculated based on also the TR peak velocity using Abbas formula, right ventricular fractional area change (RVFAC), and RVFAC/PASP as a measure of right ventricular-pulmonary arterial (RV-PA) coupling.

**Independent variables**

Our primary independent variable will be cfPWV, well known robust measure of central arterial stiffening. Also, the heart-femoral PWV and brachial-ankle PWV will be considered as potential independent variables which reflect different segmental arterial stiffness. The total arterial compliance may also be included as it represents the compliance of large, elastic central arteries and relatively small, muscular peripheral arteries as oppose to its segmental representation by PWV. As a measure of hemodynamic property, estimated central pulse pressure will also be considered as an independent variable to assess the association between central pressure pulsatility and pulmonary vasculature.

**Potential mediator variables**

Measures of LV structure (dimension, volumes, wall thickness, mass, relative wall thickness), LV systolic function (LVEF, longitudinal and circumferential strains), and LV diastolic function and filling pressure (E/A ratio, TDI e’, ratio of E wave to e’ (E/e’), and left atrial volume index).

**Other covariates** Demographic and clinical variables, assessed at Visit 5, include age, sex, race, body mass index, medication use, smoking status, blood pressure, hemoglobin A1c, serum high density lipoprotein, and serum low density lipoprotein.

**Data Analysis:**

For tabular display, clinical, echocardiographic, and pulmonary hemodynamic variables will be described by quartiles of cfPWV. Trends across cfPWV quartiles will be assessed using univariable and multivariable linear or logistic regression (e.g. adjusted for age, sex, and race).

The continuous association of cfPWV with pulmonary vascular measures will be primarily analyzed. The continuous association between cfPWV and pulmonary vascular measures will be assessed using univariable and multivariable linear regression. Potential non-linear associations between cfPWV and dependent variables will be assessed using polynomial terms in regression models, and using restricted cubic splines. Two multivariable models will be built. The first will adjust for demographics (age, sex, race). The second model will additionally adjust for echocardiographic measures of LV structure, systolic function, and diastolic function found to be
associated with cfPWV. Numeric value of coefficients for cfPWV will be presented along with p-values and confidence intervals obtained from both models. The relative difference in the two coefficients will be presented, and associated confidence bands will be generated using bootstrapping.

**Anticipated methodologic limitations:**
As this study is a cross-sectional designed study, we cannot specify causality in any of the described relationships. cfPWV may not fully capture early alterations in systemic arterial function. Similarly, echocardiographic measures of pulmonary hemodynamics are not uniformly available in the study sample. To the extent this is not missing at random, this may result in inclusion bias. We will compare those with available pulmonary hemodynamic data to those with no data, and if important differences are noted will consider additional sensitivity analyses using inverse probability of attrition weighting. Furthermore, echocardiographic measures of pulmonary hemodynamics have been validated against invasive hemodynamic measures, but remain estimations and may result in misclassification. Finally, residual confounding may remain despite of full adjustment in multivariable model.

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)?

#2048 Cheng S., et al., Association of Myocardial Deformational Measures and Arterial Stiffness in the Community
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.cscs.unc.edu/aric/forms/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscs.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.
References:


