ARIC Manuscript Proposal #2531

PC Reviewed: 4/14/15 Status: A Priority: 2
SC Reviewed: _____ Status: _____ Priority: ____

1.a. Full Title: Ventricular-arterial coupling in elderly people. The ARIC study

1.b. Abbreviated Title: VAC and elderly

2. Writing Group:
Writing group members: Miguel M Fernandes-Silva, Amil M Shah, Susan Cheng, Barry Borlaug, Carolyn Lam, Wilson Nadruz Junior, Brian Claggett, Scott D. Solomon; Others welcome.

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

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3. Timeline: Analysis will begin following proposal approval with the aim of completing analysis and a manuscript within 6 months.

4. Rationale:

Abnormalities in ventricular-arterial coupling have been implicated in the development[1] and prognosis of HF[2]. Noninvasive methods were developed to estimate arterial elastance (Ea), left ventricle end-systolic elastance(Ees)[3], allowing for the assessment of ventricular-arterial coupling in population-based studies. Both cross-sectional and longitudinal studies have shown that left ventricular (LV) stiffness and arterial stiffness increase with age [4, 5]. Coupled ventricular and arterial stiffening may underlie many cardiovascular diseases related to the aging process, including arterial hypertension and HF with preserved ejection fraction (HFPEF) [1, 6, 7]. However, ventricular-arterial coupling has not been well characterized in the elderly.

Because ventricular arterial coupling is thought to be a precursor to HF, and HFPEF in particular, ventricular arterial coupling may be particularly important among specific subgroups among whom the incidence of HF is high.,[8] Women comprise the majority of HFPEF cases in the community, and age-related ventricular-arterial stiffening is more pronounced in women.[9] Blacks have higher incidence of cardiovascular disease and higher prevalence of arterial hypertension compared to whites[10], but data are lacking regarding race-differences in ventricular-arterial coupling. Age-related stiffening also appears to be related to central obesity[9]. However, the extent to which body composition or metabolic syndrome contribute to the development of ventricular-arterial coupling is not known. The study of ventricular-arterial coupling in the Atherosclerosis Risk in Community (ARIC) study offers a unique opportunity to characterize the ventricular and arterial stiffness in a largely bi-racial population at advanced age, helping to better understand its relation with aging, gender, race.

Aim:

To characterize arterial elastance, LV end-systolic elastance and ventricular-arterial coupling in ARIC cohort.

5. Main Hypothesis/Study Questions:

1. We hypothesize that, among the elderly ARIC participants at visit 5, women will have higher measurements of arterial stiffness and left ventricular stiffness than men, and that black participants will have higher measurements of arterial stiffness and left ventricular stiffness than whites.

2. We hypothesize that the measurements of arterial stiffness and left ventricular stiffness will have a positive relationship with age, with a steeper increasing in women than in men, and in black than in white participants.

3. We also hypothesize that concurrent as well as antecedent burden of cardiometabolic traits (including inflammation, obesity, adiposity, blood pressure elevation, and other metabolic syndrome components) are associated with higher measurements of arterial stiffness and left ventricular stiffness at visit 5.

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

This study is a cross-sectional analysis of ARIC participants at Visit 5, in addition to a longitudinal analysis of cardiometabolic traits (assessed at Visits 1 through 4) related to ventricular arterial coupling measured at Visit 5.

Inclusion/Exclusion Criteria:

ARIC participants who attended visit 5 and underwent echocardiography will be included.
We will exclude those patients with missing data for key variables (Ea, Ees, blood pressure). Participants with moderate or greater aortic valve disease or in atrial fibrillation at the time of echo will be excluded. Participants of Asian or Native American ethnicity will be excluded.

Exposure variables

1. Age at visit 5, sex, race (white or black)

2. Metabolic syndrome will be defined according to the AHA/NHLBI/NCEP/ATP3 guidelines [11]: three or more of the following risk factors: obesity (waist circumference $\geq$ 102 cm men and $\geq$ 88 cm in women); triglycerides $\geq$ 150 mg/dL or on drug treatment for elevated triglycerides; low HDL cholesterol (< 40 mg/dL in men and < 50 mg/dL in women or on drug treatment for reduced HDL-c); hypertension (BP $\geq$ 130/85 mmHg or drug treatment for hypertension); fasting glucose $\geq$100 mg/dL or drug treatment for elevated glucose.

3. Antecedent cardiometabolic traits assessed at visits 1 through 4, including measures of obesity, adiposity, fasting glucose and insulin, HOMA-IR, cholesterol, blood pressure, and C-reactive protein.

Outcome variables

1. Measurements of ventricular-arterial coupling at visit 5: arterial elastance, LV end-systolic elastance (determined by single-beat method), Ea/Ees ratio and end-diastolic elastance.

Additional covariates

1. Clinical covariates at visit 5: Blood pressure, heart rate, history of hypertension, diabetes, dyslipidemia, current and former smoking status, coronary artery disease, prior MI or

revascularization procedure, prior stroke or TIA, peripheral arterial disease, heart failure, prior hospitalization for heart failure, physical activity variables,

2. All available measurements of anthropometric, bioimpedance and body size.

3. Other echocardiographic variables at visit 5: LV geometry (LV mass and volumes), LV systolic function (LV ejection fraction, longitudinal strain, circumferential strain, preload recruitable stroke work) and LV diastolic function (E wave, A wave, E wave deceleration time, TDI E', and LA volume index).

4. Pulse wave velocity values (visit 5): carotid-femoral pulse-wave velocity

5. Laboratory values at visit 5: glucose, hemoglobin A1C, total cholesterol, triglycerides, HDL, LDL, high sensitivity troponin T, NT-proBNP, creatinine, C-reactive protein.

Analytical approach:

First, we will describe the clinical characteristics and echocardiographic variables by quartiles of Ea and Ees.

To address our first hypothesis, we will compare the mean values of Ea and Ees between genders, and between races (black and white) using t-test. We will also construct linear regression models to assess for relations of gender and race with Ea and Ees while adjusting for age, gender (in race models), race (in gender models), prevalent risk factors, measurements of LV geometry (LV mass/end diastolic volume), and LV systolic function (preload recruitable stroke work). We will also use multiplicative interaction terms to test for effect modification by gender and race in each model, and consider stratified analyses as needed.

To our second hypothesis, we will perform regression analysis with age as 5-year categories. We will construct models adjusted for gender, race, prevalent risk factors, measurements of LV geometry (LV mass/end diastolic volume), and LV systolic function (preload recruitable stroke work). To address the effect modification of gender and race on age relationship, we will use multiplicative interaction terms respectively, and perform stratified analyses as needed.

To our third hypothesis, we will use multivariable adjusted analyses to determine the relative contribution of cardiometabolic traits to gender- and race-based variation in Ea and Ees. Both concurrent (visit 5) and antecedent (visit 1 through 4) assessments of independent variables will be analyzed. We will include analyses metabolic syndrome, its component traits, and the cardiometabolic traits listed above (including C reactive protein, as a measure of inflammation).

For analyses of visit 5 covariates, cross-sectional regression models will be used. For analyses of visit 1 through 4 covariates, we will use longitudinal regression models and also consider analyses of time-averaged antecedent values and trajectory model (PROC TRAJ) for continuous variables with an adequate number of antecedent observations.

All analyses will be performed using STATA v12.1 and a P value threshold of 0.05 will be considered statistically significant (including after correcting for multiple testing).

Limitations:

One limitation of this analysis is a potential selection bias, due to the considerable non-attendance at visit 5.

Brachial measurement of blood pressure at the time of the echocardiogram will be used for calculating the Ea and Ees. This strategy is more concerning in elderly especially due to the amplification phenomena and arterial stiffness in this population.

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)?

MS#1917 - (Shah et al) Association of diastolic dysfunction with high sensitivity troponin T and NT-proBNP across left ventricular geometries in the community – A preliminary analysis from the ARIC study

MS#2431 - (Shah et al) Ideal Cardiovascular Health during Adult Life and Cardiac Structure and Function among the Elderly

MS#2454 - (Poon et al) Association of metabolic syndrome and insulin resistance with pulse wave velocity: the ARIC Study

MS#2228 - (Bello et al) The relationship between cardiac structure and function and obesity assessed by body composition contrasted with anthropomorphic measures

MS#510 - (Liao et al) Multiple metabolic syndrome (disorder) and arterial stiffness

MS#2048 - (Cheng et al) Association of Myocardial Deformational Measures and Arterial Stiffness in the Community

MS#2218 – (Cheng et al) Association of Blood Pressure Burden with Cardiac Structure and Function and Incident Heart Failure in the Community

MS#1970 - (Meyer et al) Descriptive Epidemiology of Pulse Wave Velocity in the Atherosclerosis Risk in Communities (ARIC) Study

MS#2297 (Loehr et al) The association of diabetes, impaired glucose tolerance, and chronic hyperglycemia with pulse wave velocity: the ARIC study

MS#2156 (Caughey et al) Associations between arterial compliance, incident cardiovascular disease, and mortality in African Americans in the ARIC study, using a simplified echocardiographic method

MS#2054 (Gupta et al) The association of insulin resistance and glucose levels with cardiac structure and function in an older population without diabetes mellitus: The ARIC study

MS# 1032 (Kshirsagar et al) C-Reactive Protein and the Change in Blood Pressure among Individuals Initially without Hypertension

MS#1538 (Tian et al) C-Reactive Protein and the Change in Blood Pressure among Individuals Initially without Hypertension

MS#1504 (Folson et al) CRP, WBC and Heart Failure Incidence

MS#1883 (Vardeny et al) The association of Insulin Resistance with Incident Heart Failure: the Atherosclerosis Risk in Communities (ARIC) study

MS#1125 (Loehr et al) Diabetes, obesity and insulin resistance as risk factors for incident hospitalized heart failure: The Atherosclerosis Risk in Communities (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.cscc.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.cscc.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

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4. Redfield, M.M., et al., Age- and gender-related ventricular-vascular stiffening: a community-based study. Circulation, 2005. 112(15): p. 2254-62.

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11. Grundy, S.M., et al., Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation, 2005. 112(17): p. 2735-52.