

## ARIC Manuscript Proposal #2156

PC Reviewed: 06/11/13  
SC Reviewed: \_\_\_\_\_

Status: A  
Status: \_\_\_\_\_

Priority: 2  
Priority: \_\_\_\_\_

**1.a. Full Title:** Associations between arterial compliance, incident cardiovascular disease, and mortality in African Americans in the ARIC study, using a simplified echocardiographic method

**b. Abbreviated Title (Length 26 characters):** Echocardiography, arterial compliance

### 2. Writing Group:

Writing group members: Melissa Caughey, Laura Loehr, Christy Avery, Ervin Fox, Susan Cheng, Scott Solomon, Alan Hinderliter, others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. MC **[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 to be completed by October, 2013, and manuscript to be drafted by July, 2014.

#### 4. Rationale:

Decreased arterial compliance has been shown to predict adverse cardiovascular events<sup>1,2</sup>, and incident hypertension<sup>3-5</sup>. Greater arterial stiffening has been observed in African Americans, which appears to manifest at an earlier age than in Caucasians<sup>6</sup>. However, little is known of the prognostic impact of decreased arterial compliance in African Americans free of cardiovascular disease.

Several noninvasive techniques for assessing arterial compliance exist. These include carotid ultrasound distensibility with intima-medial thickness measurements, carotid-femoral pulse wave velocity, and echocardiographic stroke volume to pulse pressure ratio<sup>7</sup>. Of the three, only echocardiograms are routinely performed in clinical practice. Yet, echocardiography-derived arterial compliance has not previously been quantified in the ARIC study. Echocardiography-derived arterial compliance is easily calculated with the following formulas:

$$\text{Cross-sectional area of the left ventricular outflow tract (CSA}_{\text{LVOT}}) = (\text{LVOT radius})^2 * 3.14$$

$$\text{Left ventricular stroke volume} = \text{LVOT velocity time-integral (VTI)} * \text{CSA}_{\text{LVOT}}$$

$$\text{Pulse pressure} = (\text{systolic brachial blood pressure} - \text{diastolic brachial blood pressure})$$

$$\text{Body surface area (BSA)} = \text{SQRT} ([\text{Height(cm)} * \text{Weight(kg)}] / 3600)$$

$$\text{Echocardiography-derived arterial compliance}^8 = (\text{SV} / \text{BSA}) / \text{PP}$$

However, the left ventricular outflow tract diameter is a potential source of measurement error, which is influenced by transducer angulation, choice of measurement location along the outflow tract, and poor image quality<sup>9</sup>. Measurement errors of the LVOT diameter are compounded by squaring the radius when calculating the cross sectional area<sup>9</sup>. As a result, the LVOT velocity-time integral has been recommended as a surrogate measurement for stroke volume<sup>10</sup>.

Echocardiograms were performed at visit 3 (1993-1996) in African American participants at the Jackson site (N=2445). While LVOT velocity-time integrals were quantified in all but 8% of the echocardiograms, the LVOT diameter could not be adequately measured in 74% of the echocardiograms. We propose a simplified calculation of arterial compliance, substituting left ventricular stroke volume with LVOT velocity-time integral. We will analyze associations between arterial compliance, cardiovascular disease, and mortality in African American participants free of cardiovascular disease at visit 3 and followed for 20 years. Incident cardiovascular disease will include heart failure, coronary disease, and stroke.

A complete-case sensitivity analysis among the subset of participants with measureable LVOT diameters (N=624) will be conducted, to determine agreement between the simplified arterial compliance measurement and the stroke volume-derived measurement, in their associations with incident cardiovascular disease and mortality.

A second sensitivity analysis will be conducted by multiple imputation of missing stroke volume variables, using Markov Chain Monte Carlo methods<sup>11</sup>. Stroke volume measurements are presumed to be missing at random, and highly correlated with existing measurements of cardiac structure and function, participant demographics, and clinical characteristics.

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

What is the association between echocardiography-derived measures of arterial compliance incident cardiovascular disease, and mortality, in African Americans free of cardiovascular disease?

How well do arterial compliance calculations based on the LVOT velocity-time integral agree with arterial compliance calculations based on left ventricular stroke volume, in association with hazard ratios for incident cardiovascular disease and mortality?

## **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).**

This will be a longitudinal assessment of the association between arterial compliance, incident cardiovascular disease, and mortality in the Jackson cohort of the ARIC study. Individuals with known cardiovascular disease at visit 3 and those not participating in the echocardiography study will be excluded from the analysis. Due to the large proportion of echocardiograms with missing LVOT diameters, we will calculate arterial compliance by substituting the LVOT velocity-time integral for the left ventricular stroke volume.

Associations between arterial compliance and incident cardiovascular disease will be analyzed by Cox regression. Associations between arterial compliance and mortality will be analyzed by Cox regression as well.

To calculate arterial compliance, we request several variables from the ECHA dataset: Doppler aortic outflow velocity time integral (ECHA61), left ventricular stroke volume (ECHA65), calculated body surface area (ECHA6), systolic blood pressure (ECHA7), and diastolic blood pressure (ECHA8). Covariates for our analysis will include age, sex, smoking, glomerular filtration rate, hypertension, total cholesterol, and fasting glucose. Outcomes will include incident heart failure, stroke, or coronary disease, and mortality.

To conduct multiple imputation of missing stroke volume measurements, we will determine correlations between stroke volume and measurements of cardiac structure, indices of cardiac function, participant demographics, and clinical covariates. We will enter all variables from the survival analysis into the prediction model, as well as mitral regurgitation (ECHA17), aortic regurgitation (ECHA18), left ventricular septal thickness at diastole and systole (ECHA49 and ECHA50), left ventricular diameter at diastole and systole (ECHA51 and ECHA52), left ventricular posterior wall thickness at diastole and systole (ECHA56 and ECHA57), left atrium diameter (ECHA56), aortic root diameter (ECHA57), left ventricular mass (ECHA58), left ventricular fractional shortening (ECHA53), Doppler aortic outflow mean velocity and peak velocity (ECHA59 and ECHA60), Doppler of aortic outflow velocity-time integral (ECHA61), left ventricular outflow tract diameter (ECHA64), Doppler of mitral E wave and A wave peak velocities (ECHA68 and ECHA69), and Doppler ratio of mitral E to A wave (ECHA70). Predictors will be determined by stepwise regression, and values for missing stroke volume variables will be imputed, based on correlations with existing variables. Imputed values will be randomly selected from probabilistic distributions, and multiple datasets will be generated, incorporating imputed values. These datasets will then be combined and analyzed using Markov Chain Monte Carlo methods.

**7.a. Will the data be used for non-CVD analysis in this manuscript?**     Yes  
 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 ICTDER 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     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.csc.unc.edu/ARIC/search.php>

Yes     No



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