ARIC Manuscript Proposal #2092

PC Reviewed: 3/12/13    Status: A    Priority: 2
SC Reviewed: _________    Status: _____    Priority: ____

1.a. Full Title:

Association of Age with Diastolic Dysfunction in the Community

b. Abbreviated Title (Length 26 characters):

Age and Diastolic Dysfunction

2. Writing Group:

Writing group members:

Susan Cheng, Amil Shah, Brian Claggett, Hicham Skali, Dalane Kitzman, Scott Solomon, and OTHERS WELCOME

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ___SC__

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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:**

   Analyses to begin Spring 2013.
   A manuscript draft is expected during Summer 2013 / Fall 2013.

4. **Rationale:**

   It has been long recognized that left ventricular (LV) diastolic function progressively declines with age even after accounting for prevalent hypertension and increased LV mass, both of which are also established correlates of diastolic dysfunction.\(^{1-3}\) Because of the well-known relationship between advanced age and diastolic dysfunction, American and European guidelines recommend that echocardiographic measures of diastolic function be adjusted for age.\(^4,5\) For example, these guidelines propose that normal values for tissue Doppler-derived lateral E’ are 16.1±2.3 cm/s for persons aged 41-60 years and 12.9±3.5 for persons aged >60 years. However, the extent to which progressive impairment in LV diastolic function is part of the ‘normal aging’ process remains unclear.\(^3,6-9\) Therefore, we propose to conduct a comprehensive investigation of the association of age with echocardiographic measures of diastolic function in the Atherosclerosis Risk in Communities (ARIC) Study cohort. In doing so, we will carefully consider a variety of possible (demographic, clinical, and echocardiographic) contributors to the consistently observed phenomenon of ‘age-based diastolic dysfunction’. In a healthy aging sample of the ARIC cohort, we will also identify age-appropriate values of diastolic functional indices.

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

   Our main hypothesis is that while the aging process itself may contribute to observed age-based reduction in diastolic function, a substantial portion of this reduction may also be attributed to identifiable excess exposure to antecedent risk factors such as elevated blood pressure.

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).**

   The study sample will include individuals who attended the ARIC Visit 5 examination, who underwent echocardiography at this visit, and were free of prevalent cardiovascular disease (history of coronary heart disease, TIA/stroke, or heart failure), valvular disease (moderate or severe), or atrial fibrillation at this visit.

   **Dependent variables.** The primary dependent variables of interest will include: septal and lateral tissue Doppler-derived E’, deceleration time, E/A ratio, and E/E’ ratio. We will also consider conventionally defined grades of diastolic dysfunction.\(^4,5\)

   **Independent variables.** The primary independent variable of interest will include: age, sex, race, body mass index, blood pressure (BP) components (SBP, DBP, PP, and MAP), prevalent hypertension (BP ≥140/90 mmHg or taking anti-hypertensive medication), diabetes, smoking status, total/HDL cholesterol ratio, eGFR, LV end-diastolic diameter, LV wall thickness, LV mass, and LV relative wall thickness (LV wall thickness divided by LV end-diastolic diameter).
Additional independent variables of interest will include variables that capture antecedent burden of elevated BP, including: time-averaged BP measures (SBP, DBP, PP, and MAP) from visits 1 through 5 (with and without imputed BP values based on concurrent anti-hypertensive medication use\textsuperscript{10}), and total years with documented hypertension since visit 1 (with and without anti-hypertensive treatment, given its known effect on diastolic function\textsuperscript{11,12}).

**Analytical approach.** We will perform initial descriptive analyses including unadjusted analyses of the relations between each of the independent variables with the dependent variables. To minimize any penalty for multiple testing, we will consider E’ as the primary dependent variable. We will then perform multivariable adjusted regression analyses to examine the association of independent variables with measures of diastolic function (primarily outcome variable: E’). Relative contributions of independent variables to variation in diastolic function will be evaluated using the partial $R^2$ value for each term in the model, in addition to a calculated population attributable risk percent for covariates that may be dichotomized (as has been done previously\textsuperscript{6} and using validated methods\textsuperscript{13}). The relative contributions of prevalent and antecedent burden of elevated BP will be evaluated in separate models. We will perform analyses in the total sample as well as in the sample stratified by age group (defined by quartiles).

**Secondary analyses.** In secondary analyses, we will use multiplicative interaction terms to assess for effect modification by sex, race, and hypertension status. We will perform stratified analyses for any covariates demonstrating significant effect modification. Whereas LV relative wall thickness is a continuous measure of LV geometry, we will also consider conducting analyses using categorical definitions of LV geometry (i.e. normal, concentric remodeling, concentric hypertrophy, and eccentric hypertrophy), as previously defined.\textsuperscript{14} Of the total study sample, we will also identify a healthy subset (also free of hypertension, diabetes, eGFR<60, and BMI $\geq$30 kg/m\textsuperscript{2}), and determine reference values by age (5-10 year categories) and sex, using both empiric and quantile regression estimates.\textsuperscript{15}

All analyses will be performed using STATA v11.2 (StataCorp, College Station, TX).

**Limitations and challenges.** Because these analyses will be essentially cross-sectional, causal relationships cannot be inferred.

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  ____x__ 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 #1943 (Shah) Performance of two echocardiographic schema for grading diastolic dysfunction in an elderly community-based cohort.

MS #1917 (Shah) Association of diastolic dysfunction with high sensitivity troponin T and NT-proBNP across left ventricular geometries in the community.

MS #1953 (Shah) The relationship between concentric remodeling and left ventricular function.


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/

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


