ARIC Manuscript Proposal #2093

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

1.a. Full Title:

Characterizing Healthy Cardiac Aging and Its Correlates in the Community

b. Abbreviated Title (Length 26 characters):

Healthy Cardiac Aging

2. Writing Group:

Writing group members:

Susan Cheng, Amil Shah, Brian Claggett, Hicham Skali, Suma Konety, David Couper, Dalane Kitzman, Aaron Folsom, 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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3. **Timeline:** Analyses to begin Spring 2013. A manuscript draft is expected during Summer 2013 / Fall 2013.

4. **Rationale:**

In numerous large population-based studies, advancing age has been associated with now well-described alterations in cardiac structure and function. These classic age-related cardiac phenotypes include increase in parameters of left ventricular (LV) concentric remodeling, increase in overall LV mass, decrease in LV cavity dimensions, increase in LV ejection fraction, increase in aortic root diameter, increase in left atrial (LA) size, and more impaired LV diastolic function.\(^1\)\(^-\)\(^8\) There are also data suggesting that older age is associated with novel measures of cardiac function, including worse LV systolic strain and worse in LV diastolic strain rate.\(^9\)

Whereas much attention has been focused on abnormalities in cardiac structure and function that are often seen with aging, there are scant data on what characterizes a ‘healthy’ cardiac aging phenotype and the correlates of such a phenotype. Therefore, we propose to conduct a comprehensive study of the total ARIC study sample with echocardiography at Visit 5, and identify older individuals who demonstrate completely ‘normal’ parameters of cardiac structure and function as defined by American Society of Echocardiography (ASE) guidelines.\(^10\)\(^,\)\(^11\) We will also investigate the degree to which a healthy cardiovascular risk profile, including absence of or minimal antecedent exposure to traditional risk factors, is associated with a healthy cardiac aging phenotype. In secondary follow-up analyses, we will also assess the degree to a more optimal cardiovascular risk profile, as defined by the American Heart Association ‘ideal health score’,\(^12\) at prior visits is associated with having a ‘healthy’ cardiac profile at Visit 5.

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

Our main hypothesis is that very few older adults attending the ARIC Visit 5 examination with echocardiography will have parameters of cardiac structure and function that are considered ‘normal’ according to consensus guidelines. We hypothesize that these few older individuals who do meet these criteria represent a particularly healthy subset of the total study sample, are less likely to have had antecedent exposure to traditional risk factors, and are more likely to have had an ‘ideal’ cardiovascular health profile at examinations prior to 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 methodologic limitations or challenges if present).**

The study sample will include individuals who attended the ARIC Visit 5 examination, who underwent echocardiography while free of prevalent cardiovascular disease (coronary heart disease, TIA/stroke, or heart failure) at this visit. For analyses that require derivations of reference values not previously reported in the literature, we will define ‘normal’ as being within the interquartile range of values from healthy subset of our study sample (free of CHD, heart failure, TIA/stroke, atrial fibrillation, at least moderate valvular disease, hypertension, diabetes, eGFR<60, and BMI≥30 kg/m\(^2\)).
**Dependent variables.** The primary dependent variable of interest will include a composite score of ‘normal’ cardiac structure and function (1 point for each criterion), based on reference values defined by the ASE\textsuperscript{10,11} guidelines for: LV mass, LV wall thickness, relative wall thickness, LV end-diastolic dimension, LV volumes, aortic root diameter (indexed to body surface area), LA volume (indexed to body surface area), LV ejection fraction, LV diastolic function (using ASE criteria for defining dysfunction), and LV systolic strain and diastolic strain rate (with normal values defined as within the interquartile range of a healthy reference sample). Secondary dependent variables will include each of the above listed parameters of cardiac structure and function analyzed separately.

**Independent variables.** The primary independent variables of interest will include: age, sex, race, body mass index, blood pressure (BP) components (SBP, DBP, PP, and MAP), prevalent hypertension (BP $\geq$140/90 mmHg or taking anti-hypertensive medication), diabetes, smoking status, total/HDL cholesterol ratio, and eGFR. Additional independent variables of interest will include variables that capture antecedent burden of risk exposure, 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{13}), and total years with documented hypertension since visit 1 (with and without anti-hypertensive treatment); time-averaged total/HDL cholesterol (with and without cholesterol-lowering treatment) and total years with documented hypercholesterolemia (total cholesterol $>$200 mg/dL or taking lipid-lowering treatment); total years of documented antecedent smoking; time-averaged body mass index, and total years with documented obesity; and, time-averaged fasting glucose, and total years with documented diabetes; and, time-averaged eGFR. In secondary analyses, and in separate models, we will consider as independent (predictor) variables the American Heart Association ‘ideal cardiovascular health’ score,\textsuperscript{14} as assessed at prior ARIC examinations including Visit 1.\textsuperscript{12} This ‘ideal cardiovascular health’ score is an ordinal measure of cardiovascular risk burden defined according to ‘ideal’ criteria that has been defined previously in ARIC and elsewhere.\textsuperscript{12,14}

**Analytical approach.** We will perform initial descriptive analyses including unadjusted analyses of the relations between each of the independent variables with the primary dependent variable (i.e. ‘healthy cardiac phenotype’ score). Depending on the distribution of the primary variable, we may consider dichotomizing this variable and using logistic regression analyses. We will then perform multivariable adjusted analyses to examine the association of independent variables with the primary dependent variable. Relative contributions of independent variables to presence of each outcome variable will be evaluated using the partial $R^2$ value for each term in the model. The associations of prevalent and antecedent burden of risk exposures will be evaluated in separate models.

**Secondary analyses.** In secondary analyses, we will use multiplicative interaction terms to assess for effect modification by age, sex, race, and hypertension status (where appropriate, as reference values for some echo parameters are sex-specific). We will perform stratified analyses for any covariates demonstrating significant effect modification. We will also consider analyzing select component dependent variables in separate logistic regression models for each. Whereas LV relative wall thickness is a continuous measure of LV geometry, we will also consider conducting analyses where ‘normal LV geometry’ is defined categorically (i.e. normal,
concentric remodeling, concentric hypertrophy, and eccentric hypertrophy), according to published criteria.\textsuperscript{15} In secondary analyses, we will also consider using an aggregate score of antecedent cardiovascular risk burden represented by the American Heart Association ‘ideal cardiovascular health’ score,\textsuperscript{14} as previously defined and computed based on available ARIC data at Visit 1.\textsuperscript{12} We will consider using available ARIC data at Visits 2 through 4 to similarly compute the ‘ideal cardiovascular health’ score at these visits, and analyzing the association of consistently optimal scores (or time-averaged scores) with having a healthy cardiac phenotype at Visit 5.

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

Limitations and challenges. Because the primary analyses will be essentially cross-sectional, causal relationships cannot be inferred. The secondary longitudinal analyses pertaining to outcomes will need to await a longer follow-up period during which an adequate number of events for analyses have accrued.

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)?

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.cscn.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

