ARIC Manuscript Proposal #2770

PC Reviewed: 6/7/16  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Ventricular-arterial coupling and incidence of heart failure. The ARIC study

1.b. Abbreviated Title: VAC and incident HF

2. Writing Group:

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __MMF__ [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 6 months.
4. Rationale:

Heart failure (HF) affects more than five million people in the United States and carries high morbidity and mortality.\(^1\) Advances in therapeutics improved survival of patients with HF and occurred in parallel of better understanding of mechanisms of HF.\(^2\) Even so, mortality remains high among patients with HF, which underscores the need for further improvement in comprehending the pathophysiology of HF, particularly HF with preserved ejection fraction (HFPEF), for which no therapy has been proven to improve survival.

Abnormalities in ventricular-arterial coupling have been implicated in the development and progression of HF.\(^3\) Ventricular arterial coupling is determined by the ratio between arterial elastance (Ea) and left ventricle end-systolic elastance (Ees), which can be measured by noninvasive methods, allowing for its assessment in population-based studies.\(^4\) Previous studies have shown patients with HF have abnormal ventricular arterial coupling. Patients with HFPEF display high Ea and Ees, reflecting high arterial and ventricular stiffness, respectively, compared with individuals without HF.\(^3\) In the community, ventricular arterial stiffness increases with age and is higher among women, suggesting that ventricular-arterial stiffness may contribute to the higher prevalence of HFPEF among elderly and among women.\(^5\) However, it is unknown whether individuals with abnormal ventricular arterial coupling in the community are at increased risk of HF. The Atherosclerosis Risk in Community (ARIC) study offers a unique opportunity to evaluate whether measures of Ea, Ees and Ea/Ees ratio are associated with increased risk of developing HF.

Aim:

To investigate whether abnormalities in ventricular-arterial coupling are associated with higher incidence of HF or death in the community.

5. Main Hypothesis/Study Questions:

We hypothesize that, among the elderly ARIC participants at visit 5, Ea, Ees and Ea/Ees ratio will be associated with the incidence of HF or all-cause death during the follow-up.

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 longitudinal analysis of ARIC participants starting 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). Participants with prevalent HF at visit 5, moderate or greater aortic valve disease, in atrial fibrillation at the time of echo or with Asian or Native American ethnicity will be excluded.

Exposure variables
Measurements of ventricular-arterial coupling at visit 5: Ea, left ventricle Ees (determined by single-beat method), and Ea/Ees ratio.

Outcome variables
1. Composite outcome of incident HF or all-cause death.
2. Incident HF was defined by HF hospitalization after visit 5, with ICD-9 code 428x in any position, obtained by ARIC study retrospective surveillance of hospital discharges.
3. Deaths were ascertained through linkage with the National Death Index.

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 and socioeconomic status variables, including income and education level.
2. 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).
3. Pulse wave velocity values (visit 5): carotid-femoral pulse-wave velocity
4. 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:
To access our main hypothesis, we will build Cox proportional hazard regression models for the associations of Ea, Ees and Ea/Ees ratio with the composite outcome, HF incidence and all-cause death, starting the follow-up at the echocardiogram date. We will construct models adjusting for age, sex, race, blood pressure, prevalent risk factors, and echocardiographic measures of cardiac structure and function. To test for non-linear relationships between the predictors and the incidence of outcomes, we will further build Cox regression models using restricted cubic splines. We will also test for effect modification by gender and race using multiplicative interaction terms, and consider stratified analyses as needed. All analyses will be performed using STATA v13.1 and a \( p \) value threshold of 0.05 will be considered statistically significant.

Limitations:

This analysis may represent a healthier population than the original ARIC cohort due to survivor bias and the considerable non-attendance at visit 5.

Although they were validated, noninvasive methods to assess Ea and Ees have greater variability compared with invasive measurements.

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.cscu.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#2531 - (Fernandes-Silva et al) Ventricular-arterial coupling in elderly people. The ARIC study

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#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

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)* #946)

*ancillary studies are listed by number at http://www.csc.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.csc.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


