ARIC Manuscript Proposal #2537

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

1. Full Title: The Systolic Ejection Time as predictor of cardiovascular morbidity and mortality in African-Americans in the Atherosclerosis Risk in Communities Study

   b. Abbreviated Title (Length 26 characters): SET, Echo, cardiovascular morbidity and mortality

2. Writing Group:
   Writing group members: Tor Biering-Sorensen, Gabriela Querejeta Roca, Sheila Hegde, Amil Shah, Brian Claggett, Thomas H. Mosley, Jr., Kenneth R. Butler, [Others welcome], Scott D. Solomon

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _TBS_ [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 of data becoming available.

4. **Rationale:**
   The cardiac time intervals are defined by the opening and closing of the valves of the heart, which in turn is determined by pressure differences across the valves. All clinicians are familiar with audible assessing the cardiac time intervals. By using their stethoscope, audible changes in the cardiac time intervals can be assessed. Preservation of normal cardiac time intervals is intimately related to normal cardiac physiology, hemodynamics, mechanics and biochemistry.

In the ailing myocardium, the cardiac time intervals will change during disease progression\(^1\)–\(^5\). As left ventricular (LV) systolic function deteriorates, the time it takes for myocardial myocytes to achieve an LV pressure equal to that of aorta increases, resulting in a prolongation of isovolumic contraction time\(^5\). Furthermore, the ability of myocardial myocytes to maintain the LV pressure decreases, resulting in reduction in the systolic ejection time (SET)\(^5\). Therefore, the cardiac time intervals, may be useful to identify subtle impairments in the cardiac function, which are unnoticed by conventional echocardiography\(^6,7\). This echocardiographic parameter may thus identify patients in high risk of future fulminant cardiovascular disease.

Previous studies, which have evaluated the prognostic value of the cardiac time intervals and the combined index of cardiac time intervals, the myocardial performance index, have been performed in selected populations, e.g., patients after acute myocardial infarction\(^8\)–\(^10\), elderly men\(^11\), patients with cardiac amyloidosis\(^12\), with idiopathic-dilated cardiomyopathy\(^13\), with isolated diastolic dysfunction\(^14\), and in patients with systolic heart failure\(^15\). Additionally, the cardiac time intervals have been demonstrated to provide prognostic information incremental to the conventional echocardiographic measures of cardiac structure and function in several studies\(^10,11,16\). No studies have, however, tested the prognostic significance of the SET to predict cardiovascular morbidity and mortality in African Americans.

5. **Main Hypothesis/Study Questions:**
   The study questions below will explore whether SET is a predictor of incident heart failure and cardiovascular events, controlling for covariates for incident heart failure in African Americans:

   1. To estimate the association of SET with incident heart failure in African Americans
   2. To estimate the association of SET with ischemic cardiovascular disease in African Americans
   3. To estimate the association of SET with mortality in African Americans
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 study of ARIC cohort participants beginning at visit 3 because this is the visit when echocardiography was performed in the Jackson participants.

Study population
To be included in the analysis the participant must have undergone echocardiography and have the systolic ejection time measured.
Exclusion criteria include:
- Prevalent or missing HF status at visit 3
- Missing covariate data (age, gender, heart rate, BMI, hypertension, diabetes, prevalent coronary heart disease, systolic and diastolic blood pressure, fractional shortening)

Prevalent HF at visit 3 will be defined as those who had prevalent HF at visit 1 (by Gothenburg Criteria or use of HF medications) or those with incident HF between visits 1 and 3.

Exposure and covariates
Participants will be categorized according to SET quartiles in table 1. Clinical characteristics, echocardiographic cardiac structure and function, and outcomes (incident HF, MI and mortality) will be compared between categories of SET, based upon data variables collected at visit 3. In particular, clinical variables to be evaluated include: age, sex, hypertension, diabetes mellitus, coronary artery disease, interim myocardial infarction, lipid levels, smoking status, body mass index, and blood pressure. Echocardiographic variables to be evaluated include: left atrial size, left ventricular (LV) size, aortic root dimension, LV fractional shortening and ejection fraction, valvular disease, mitral annular calcification, aortic valve fibrosis, LV wall thickness, LV mass, LV geometry, LV stroke volume and cardiac output, Doppler mitral inflow E and A wave peak velocities, and E/A ratio.

Outcome
The primary outcomes of interest will be incident heart failure, myocardial infarction and all-cause mortality. The follow up period will be defined as the time elapsed from the visit 3 date to the date of incident HF, MI or mortality date of last contact for those lost to follow-up, or December 31, 2011.

Statistical analyses:
Categorical variables will be compared via \( \chi^2 \) and continuous data will be compared between groups via a non parametric trend test. \( P \) values < 0.05 will be considered significant. Incidence rates for heart failure, MI and mortality will be calculated as number of events divided by person time at risk and will be stratified by category of SET. Time to event analysis will be performed according to the Kaplan Meier method with the
log-rank test used to assess for differences. Univariate and multivariate hazard ratios for incident heart failure will be estimated using Cox proportional hazards regression. Univariable and multivariable linear and logistic regression analysis will be used to assess associations between SET as a continuous and categorical variables and echocardiographic characteristics. Adjustments for differences in clinical characteristics (based upon P <0.05 and/or clinically important covariates) will be performed. Effect modification by gender and LVEF will also be tested. Sensitivity analyses excluding those participants with prevalent coronary artery disease at baseline will also be performed.

Limitations
SET will only be assessed at visit 3 and thus the association between SET and incident heart failure, MI and mortality would not take into account the SET at the time of incident HF event. Incident HF and MI will be defined from ICD codes from hospitalization discharge summaries that were not further adjudicated. However, this definition has been previously validated and utilized in ARIC. Echocardiographic data is based upon M-mode, 2 dimensional, and blood flow Doppler measurements. Thus, ejection fraction and grading of diastolic function will not be assessed using current American Society of Echocardiography recommendations. Nevertheless, Teichholz’ method for LVEF has previously been validated and transmitral E and A wave velocities and the E/A ratio to describe diastolic function have been previously published from ARIC.

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 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 ___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.csc.c.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)?


*This proposal seeks to explore whether echo variables of LV structure and function are predictors of incident HF and CV events. For the analysis proposed, we intend to look at the systolic ejection time as a predictor of cardiovascular morbidity and mortality. This measure was not included in the previous proposal.

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.cscce.unc.edu/aric/forms/](http://www.cscce.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/](http://publicaccess.nih.gov/) are posted in [http://www.cscce.unc.edu/aric/index.php](http://www.cscce.unc.edu/aric/index.php), under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit_process_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.
References


