ARIC Manuscript Proposal #

PC Reviewed: 10/9/12  Status: A  Priority: 2
SC Reviewed: __________  Status: _____  Priority: _____

1.a. Full Title: Electrocardiographic correlates of cardiac structure and function in elderly Americans in the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): ECG and Echo

2. Writing Group:

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __DG__ [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 elderly are at the greatest risk for the development of cardiovascular disease.\(^1\) In particular, the lifetime risk for the development of heart failure by age eighty years old is approximately 20%.\(^2\) Moreover, approximately half of all patients with heart failure have preserved left ventricular ejection fraction, in which the predominant pathophysiology is thought to be due to diastolic dysfunction. The prognostic importance of diastolic dysfunction to the development of heart failure is now well recognized\(^3,4\) and builds upon the existing literature regarding systolic dysfunction and the risk of heart failure.\(^4,7\) While the American Heart Association-American College of Cardiology Guidelines recognize these as risk factors for the development of heart failure,\(^8\) the optimal method for evaluating patients in the community remains uncertain.

The electrocardiogram is an inexpensive and readily available non invasive tool for the characterization of cardiac structure and function. For example, among patients with HF and reduced ejection fraction, increased QRS width is a marker of dyssynchrony and cardiac remodeling. However, there have been few analyses of cardiac structure and function in relation to QRS duration among patients without HF. The Framingham Heart Study found that increasing QRS duration was associated with left ventricular mass and dimensions and inversely associated with systolic function.\(^9\) In a cardiac MRI sub study of patients enrolled in the ONTARGET or TRANSCEND parallel trials, LV mass and volumes increased in relation to QRS width.\(^10\) Recently, the QT interval was demonstrated to be associated with diastolic dysfunction (as assessed by tissue Doppler E prime) in a community sample of patients undergoing echocardiography.\(^11\) This added to the existing literature regarding the relationship between the QT interval and left ventricular mass and diastolic dysfunction (assessed by transmitral Doppler E/A).\(^12,13\) Thus, readily available easily measured parameters from the ECG, such as QRS duration and QT interval, may be useful for characterizing cardiac structure and function. However, these studies included predominantly non-black or African-American populations and in the case of ONTARGET/TRANSCEND, all patients were at high cardiovascular risk based on the presence of vascular disease and/or diabetes mellitus with end organ dysfunction.

Despite the elderly being at high risk for the development of cardiovascular disease and heart failure, the associations between cardiac structure, systolic and diastolic function and ECG measures within a community dwelling bi-racial cohort of elderly Americans are not well understood. The Atherosclerosis Risk in Communities study is well-suited to address this gap by utilizing the electrocardiograms and echocardiograms performed during visit 5.

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

**Main Objectives:**

1) Describe the relationship between electrocardiographic parameters and cardiac structure
2) Describe the relationship between electrocardiographic parameters and systolic function
3) Describe the relationship between electrocardiographic parameters and diastolic function

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 cross sectional study of ARIC cohort participants at visit 5.
Study population

To be included in the analysis the participant must have undergone electrocardiography and echocardiography at visit 5 with available measurements from each test. Exclusion criteria include:

- Use of antiarrhythmic drugs at visit 5
- Missing covariate data (age, sex, race, hypertension, use of antihypertensive medications, diabetes mellitus, coronary artery disease, lipid levels, smoking status, body mass index, blood pressure, medications, hemoglobin, renal function, troponin T, and NT-proBNP)
- Wolf Parkinson White/preexcitation on ECG
- Paced rhythm

Anti-arrhythmic medication use will be identified with the Medi-Span Therapeutic Classification system (codes = 350000, 350500, 351000, 352000, 353000, 354000, and 355000). Covariates will be defined according to standard ARIC definitions. Wolf Parkinson White and Paced rhythm will be identified using the Minnesota Coding System for ECG, using codes 6-4-1 or 6-4-2 and 6-8, respectively.

Exposure and covariates

Participants will be categorized according to echocardiographic structure and function. From the echocardiogram, cardiac structure will be defined using standard categories of left ventricular geometry, namely, normal, concentric remodeling, concentric hypertrophy, or eccentric hypertrophy based upon relative wall thickness and left ventricular mass. Systolic function will be categorized according left ventricular ejection fraction (<40%, 40-55%, or ≥ 55%). Diastolic function will be assessed via tissue Doppler imaging (mitral annular E prime velocities), transmitral Doppler (E/A and E deceleration time), as well left atrial size and overall grade of diastolic function.

Electrocardiographic parameters of interest with include those that are readily clinically measured, such a heart rate, rhythm (normal sinus rhythm vs. atrial fibrillation/flutter), QRS axis, QRS voltage (by Cornell criteria), presence of left ventricular hypertrophy by Cornell criteria, QRS duration, QRS/T angle, QT interval, corrected QT interval, ST depressions, and T wave inversions. QRS duration will be further evaluated as <100, 100-109, 110-119, and ≥120 msec and those with QRS ≥120 msec will be further categorized according to the type of ventricular conduction delay, i.e. Left bundle branch block (LBBB), right bundle branch block (RBBB), RBBB with left anterior fascicular block (LAFB), or intraventricular conduction delay (IVCD) using Minnesota codes (7-1, 7-1-1, 7-1-2 for LBBB, 7-2, 7-2-1, 7-2-2 for RBBB, 7-8 for RBBB+LAFB, and 7-4 for IVCD).

Clinical, electrocardiographic, and echocardiographic characteristics will be compared across categories of LV geometry, LVEF, and diastolic function. In particular, clinical variables to be evaluated include: age, sex, race, hypertension, use of antihypertensive medications, diabetes mellitus, coronary artery disease, lipid levels, smoking status, body mass index, blood pressure, medications, hemoglobin, renal function, troponin T, and NT-proBNP. Echocardiographic variables to be evaluated include: left atrial size, left ventricular (LV) size, LV ejection fraction, LV wall thickness, LV mass, LV geometry, LV stroke volume and cardiac output, Tissue Doppler E’, Doppler mitral inflow E and A wave peak velocities, E/A ratio, E deceleration time, and LA size.
Outcome
For the relationships between ECG parameters and cardiac structure and function, the primary independent variables of interest will be electrocardiographic measures, while the dependent variables will be echocardiographic measures of cardiac structure and function.

Statistical analyses:
Distributions of variables will be assessed and non-normal continuous data will be transformed. The distributions will also be assessed for outliers.
Categorical variables will be compared via $\chi^2$ or Fischer exact test, while continuous data will be compared between groups via a non parametric trend test. Two sided P values $< 0.05$ will be considered significant.
Univariable and multivariable linear and logistic regression analysis will be used to assess associations between ECG parameters as 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, race, field center, and heart failure status will also be tested.

Limitations
Analysis of electocardiographic variables will be limited to those that are readily available and routinely measured to maintain clinical applicability. Echocardiographic measures of systolic function that will be assessed include left ventricular ejection fraction, which may not fully reflect contractile function. A future proposal from our group will examine the relationship between myocardial deformational parameters (i.e. strain) and electrocardiographic measures. Assessment and grading of diastolic function will be performed according to both the American Society of Echocardiography guidelines, as well as that of Redfield et al.\textsuperscript{14}

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.cscc.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.cscc.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:


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10. Stewart RA, Young AA, Anderson C, Teo KK, Jennings G, Cowan BR. Relationship between qrs duration and left ventricular mass and volume in patients at high cardiovascular risk. *Heart.* 2011;97:1766-1770


