ARIC Manuscript Proposal # 1815

PC Reviewed: 9/13/11 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: _____**

1.a. Full title: Beat-to-beat three-dimensional ECG variability is associated with sudden cardiac death in ARIC study population

1.b. Abbreviated title (26 char): 3D ECG in ARIC

2. **Writing group**: Larisa G. Tereshchenko, Elsayed Z Soliman, Josef Coresh, Gordon F. Tomaselli, Ronald D. Berger

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ___LT__ **[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:** Start – immediately after approval (expected, August 2011). Manuscript submission expected: January 2012.

Rationale:

Previously[1, 2] we explored a 3D approach in assessment of temporal variability of cardiac signal and showed that a relatively high T peaks cloud volume of 30 consecutive sinus beats, measured as the highest tertile of T/R peaks cloud volumes ratio, is associated with increased risk of VT/VF in patients with structural heart disease and systolic dysfunction. We have found racial differences in 3D repolarization lability, characterized by larger T/R peaks cloud volumes ratio in whites than blacks and different determinants of peaks cloud volume. In this proposed study will validate the prognostic significance of T peaks cloud volume and other 3D ECG parameters for predication of sudden cardiac death (SCD) in The Atherosclerosis Risk in Communities Study (ARIC) study population.

Main hypothesis/Study questions: We hypothesize that the 3D ECG markers of increased repolarization lability will be predictive of SCD, cardiovascular and all-cause mortality in ARIC study population. Gender- and race- specific predictive value of 3D ECG parameters will be investigated.

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).

All ARIC participants with good quality baseline digital 12-lead ECG in sinus rhythm will be eligible for inclusion in this analysis.

Magellan GE software (available at the ECG reading center) will be used for extraction of the digital .txt file of the ARIC baseline ECGs for further custom analysis. The ARIC ECG reading center PI will work with the ARIC CC to make the digital signal available for use by the lead author of the proposed work. All digital ECGs will be analyzed by customized Matlab software in a robust automated fashion. First 12-leads ECG signal will be transformed into orthogonal XYZ signal.

ECG variability analysis: the volume of R and T peaks cloud

Methodology of analysis was previously described[1, 2]. In sinus rhythm ECG 30 consecutive sinus beats were selected, and premature ventricular complexes are manually excluded. The peaks of R-waves and T-waves are detected automatically in 3D ECG through use of custom-designed software written in MATLAB (MathWorks,Inc., Natick, MA). The peak of R-waves was found as the furthest point away from the origin of the three loops. The peak of T-waves is detected automatically as the furthest point away from the origin in a time frame following the detected R-wave peak. Results are visually reviewed to ensure accuracy and quality of peaks detection. R and T peaks are plotted in 3D to form an R peaks cloud and a T peaks cloud. The peaks cloud points are used to form a convex hull, the convex shape with the smallest volume necessary to encompass all the wave peak points. The volume of the peaks cloud is calculated as the volume within the convex hull. The ratio of the T peaks cloud volume to the R peaks cloud volume is calculated. Cases of two distinct T peaks clouds are considered as positive 3D TWA.

Outcomes:

- Adjudicated definite SCD
- Cardiovascular mortality
- All-cause mortality.

The proposed predictors of SCD will be measured as continuous variables and then will be separated based on quartiles. At the same time 2.5th (97.5th) and 5th (95th) percentiles will be determined in all patients and separately in males/females, whites/non-whites. Proposed ECG markers will be categorized at threshold of 2.5th (97.5th) and 5th (95th) percentiles. Predictive value of several thresholds will be compared. Simple and multiple linear regression models will be explored to determine clinical and demographic factors that may play the role of predictors of our tested marker of interest, presented as a continuous variable. For such linear regression models, the tested marker will be an outcome variable. Continuous variables will be compared using the independent samples *t* test if normally distributed and the Wilcoxon rank sum test if skewed. The Pearson chi-square test will be used to compare categorical variables. A *p*-value of <0.05 will be considered significant. Kaplan-Meier survival analysis will be used to compute mean and median survival time, with standard error and 95% confidence interval. The log-rank (Mantel-Cox) statistic will be computed to test the equality of survival distributions. A Cox proportional hazards analysis will be performed separately for each variable of interest. Multivatiate Cox regression models will include tested ECG markers along with known clinical and demographic predictors of outcomes. ROC analysis will be performed and AUC will be calculated for every tested risk marker. Multiple ROC AUCs will be compared. Value of ECG markers, which would provide the best precision, sensitivity and specificity based on ROC analysis, will be compared with thresholds determined based on quartiles and other percentiles as described above.

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/

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.

Reference List

(1) Han L, Tereshchenko LG. Lability of R- and T-wave peaks in three-dimensional electrocardiograms in implantable cardioverter defibrillator patients with ventricular tachyarrhythmia during follow-up. *J Electrocardiol* 2010 November;43(6):577-82.

(2) Tereshchenko LG, Han L, Cheng A et al. Beat-to-beat three-dimensional ECG variability predicts ventricular arrhythmia in ICD recipients. *Heart Rhythm* 2010 November;7(11):1606-13.