

ARIC Manuscript Proposal # 1815

PC Reviewed: 7/12/11
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full title (tentative): Associations between beat-to-beat three-dimensional ECG variability and sudden cardiac death, all-cause and cardiovascular mortality in ARIC study population

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

2. Writing group: Larisa G. Tereshchenko, Elsayed Z Soliman, Joseph 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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3. Timeline: Start – immediately after approval (expected, July 2011). Manuscript submission expected: January 2012.

Rationale: Recently first author of proposed manuscript Larisa G. Tereshchenko developed new method of 3D ECG analysis for assessment of the risk of ventricular tachycardia (VT) /ventricular fibrillation (VF)(1, 2), and showed that relatively large T peaks cloud volume is associated with increased risk of VT/VF in patients with structural heart disease and systolic dysfunction and implanted ICDs for primary prevention of sudden cardiac death. We observed significant racial differences in 3D repolarization lability. Proposed study will validate predictive value of T peaks cloud volume and other 3D ECG parameters in The Atherosclerosis Risk in Communities Study (ARIC) study population and will explore gender and racial differences in repolarization.

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.

Repolarization lability is usually assessed by QT variability. Methodological difficulties, i.e., inaccuracies in the T end determination, the existence of U waves and biphasic T waves, could affect results of QT variability assessment on routine ECGs. VCG has well recognized advantages over routine surface ECG in description of repolarization(3): VCG helped to recognize 12-leads QT dispersion as an attribute of T-loop morphology, rather than dispersion of repolarization. It was also demonstrated that the T axis is associated with QT duration(3): the more perpendicular the T axis is to the lead axis, the shorter the QT duration is. Classical VCG method considers one averaged heart beat and therefore is not suggested for evaluation of rhythm disorders. In our study we merged VCG with assessment of temporal variability of loops and therefore use the term 3D ECG, but not VCG, to specify this approach. Our finding of relatively high T peaks cloud volume associated with VT/VF agrees with previous works showing increased temporal lability of repolarization as a risk factor for VA. Importantly, usual assessment of repolarization lability (QT variability) requires longer recordings. As we utilize different 3D approach, in the proposed study we will test hypothesis that 10 sec resting ECG is enough for assessment of repolarization lability in 3D ECG .

Racial differences in 3D ECG variability . In previous analysis we observed significant racial differences in 3D repolarization lability, which was more pronounced at baseline in whites than blacks. The predictive value of increased T/R peaks cloud volumes ratio was also more evident in whites.

We have found different traditional ECG parameters associated with peaks cloud volume in blacks and whites. In whites T peaks cloud volume was correlated with QRS width, i.e., more likely wide round QRS and T loops shape, and with QTv. Both these factors are known markers of increased VA risk. However, in blacks T peaks cloud volume was correlated with the HRv only, which if increased is associated with a lower risk of VA. Thus, the 3D repolarization lability portrait overall had more favorable characteristics in blacks. Changes in the autonomic cardiac regulation, either reduced sympathetic or increased vagal tone, or suggested sodium channel polymorphism among blacks(4) may provide some explanation for our findings. Even so, further studies are warranted to elucidate the mechanisms of the intriguing racial differences

in 3D ECG temporal variability. Analysis of ARIC study 3D ECG data will allow such unique opportunity.

Main hypothesis/Study questions: We hypothesize that the 3D ECG markers of increased repolarization lability are associated with 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-leads GE MUSE ECG in sinus rhythm will be eligible for inclusion in this analysis.

We will use Magellan GE software (available for the first author) for extraction of digital .txt file for further custom analysis. Digital 12-leads ECG signal will be transformed into orthogonal XYZ signal. Then digital ECGs will be analyzed by customized Matlab software in a robust automated fashion.

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:

- 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 subjects 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. Multivariate 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 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 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.unc.edu/ARIC/search.php> ___ 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 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.csc.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; 43:577-82.
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; 7:1606-13.
3. Kors JA, van HG, van Bommel JH. QT dispersion as an attribute of T-loop morphology. *Circulation* 1999; 99:1458-63.
4. Burke A, Creighton W, Mont E, et al. Role of SCN5A Y1102 polymorphism in sudden cardiac death in blacks. *Circulation* 2005; 112:798-802.