ARIC Manuscript Proposal # 1814

PC Reviewed: 7/12/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: _____**

1.a. Full title (tentative): Associations between novel ECG marker, Sum Absolute QRST integral, and sudden cardiac death, all-cause and cardiovascular mortality in ARIC study population

1.b. Abbreviated title (26 char): SAI QRST 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 markers of the risk of ventricular tachycardia (VT) /ventricular fibrillation (VF), namely sum absolute QRST integral [SAI QRST](1, 2) and showed that SAI QRST >145 mV*ms is associated with an extremely low risk of arrhythmia in structural heart disease patients with implanted ICDs for primary prevention of sudden cardiac death. In prospective observational study of primary prevention ICD patients (PROSE-ICD), SAI QRST ROC analysis exhibited a large AUC and hazard ratio in the range of 4–6, as well as high sensitivity and negative predictive value. High sensitivity carries potential of novel marker's use for screening in the populations with relatively low incidence of sudden cardiac death (SCD). Independent validation of predictive values of SAI QRST is necessary before implementation into clinical practice. Proposed study will validate predictive value of SAI QRST in The Atherosclerosis Risk in Communities Study (ARIC) study population.

Sum Absolute QRST integral (SAI QRST)

The QRST integral was conceived by Wilson et al(3) as the time integral of the heart vector(4) and expresses the heterogeneity of the AP morphology.(5) Unlike Wilson, we calculated sum absolute QRST integral to adjust our analysis to the requirements dictated by acquired filtered ECG signal characteristics. Our proposed metric has benefit of less dependence on a precise definition of the isoelectric baseline position. Our choice of analyzing orthogonal ECGs over 12-lead ECGs was based on the advantages provided by orthogonal ECGs, which permit assessment of the heart vector. Summation of absolute QRST integral of all 3 orthogonal ECG leads allows assessment of the magnitude of total cardiac electrical power and eliminates bias of single lead axis position. Proposed project will further explore the precise electrophysiological meaning of SAI QRST. We hypothesize that (1) the low SAI QRST characterizes significant cancellation of electrical forces as an important preexisting condition that may facilitate sustained VA; (2) low SAI QRST reflects reduced mass of viable myocardium in patients with structural heart disease; (3) SAI QRST characterizes specific geometry of the heart chambers.

Cancellation of forces results in low SAI QRST

Cancellation of electrical forces in the heart may reduce ECG amplitudes. An estimated 75% of the electrical energy is canceled during ventricular depolarization,(6) and 92-99% is cancelled during repolarization(7). Previous experiments showed that AP morphology gradients in different sites of the heart may have opposing directions and cancel out.(8) In computer simulations, sum QRST integral was decreased when APDs were randomly reassigned in the model.(9) Importantly, random APD assignment made the model more susceptible to ventricular fibrillation (VF) initiation. Evidently, a decrease in the sum absolute QRST integral due to cancellation coexists with the locally observed increase in APD gradients and native QRST integral, as a marker of a heterogeneity of repolarization or heterogeneity of AP morphology.(10), (11)

Diminished total cardiac electrical power results in low SAI QRST.

Experienced clinicians know that patients susceptible to VT/VF are characterized by low voltage ECGs in limb leads. Several previous studies reported, but did not emphasize their findings of diminished total cardiac electrical power. Gardner et al(11) in 1986 revealed that in body surface potential maps the peak-to-peak amplitudes are significantly diminished in patients with VA (see Table 3 in cited paper).

Main hypothesis/Study questions: We hypothesize that the SAI QRST is associated with SCD, cardiovascular and all-cause mortality in ARIC study population. Gender- and race- specific predictive value of SAI QRST 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 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. **SAI QRST – sum absolute QRST integral** will be measured as previously described(1, 2). In short, absolute QRST integral will be measured as the arithmetic sum of areas under the QRST curve (absolute area under the QRST curve above baseline will be added to the area below baseline), averaged during recorded 10 sec epoch. Baseline will be drawn automatically via the end of T wave. Fiducial points will be identified automatically by algorithm in each eligible for analysis beat during 5 min epoch. Figures will be created automatically for visual inspection to confirm appropriate placement of fiducial points. The sum magnitude of 3 orthogonal leads absolute QRST integral (SAI QRST) will be calculated. In addition, SAI QRS (arithmetic sum of areas under the QRS curve) and SAT JT (arithmetic sum of areas under the JT curve – from J point to the end of T wave) will be calculated separately.
QRST integral – sum QRST integral (∫QRST) will be measured as the algebraic sum of areas under the QRST curve (native integral), averaged during a 10-sec epoch, and the sum of 3 orthogonal leads ∫QRST will be calculated. ∫QRST was originally shown to be the marker of action potential morphology heterogeneity *in silico*.

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 2.5^{th} (97.5^{th}) and 5^{th} (95^{th}) percentiles will be determined in all subjects and separately in males/females, whites/non-whites. Proposed ECG markers will be categorized at threshold of 2.5^{th} (97.5^{th}) and 5^{th} (95^{th}) 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

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3. WILSON FN, Macleod AG, Barker PS, JOHNSTON FD. The determination and the significance of the areas of the ventricular deflections of the electrocardiogram. Am Heart J 1934;46-61.
4. BURGER HC. A theoretical elucidation of the notion ventricular gradient. Am Heart J 1957; 53:240-6.

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6. Abildskov JA, KLEIN RM. Cancellation of electrocardiographic effects during ventricular excitation. Sogo Rinsho 1962; 11:247-51.
7. Burgess MJ, Millar K, Abildskov JA. Cancellation of electrocardiographic effects during ventricular recovery. J Electrocardiol 1969; 2:101-7.
8. Urie PM, Burgess MJ, Lux RL, Wyatt RF, Abildskov JA. The electrocardiographic recognition of cardiac states at high risk of ventricular arrhythmias. An experimental study in dogs. Circ Res 1978; 42:350-8.
9. Okazaki O, Lux RL. Paradoxical QRST integral changes with ventricular repolarization dispersion. J Electrocardiol 1999; 32 Suppl:60-9.
10. Burton FL, Cobbe SM. Dispersion of ventricular repolarization and refractory period. Cardiovasc Res 2001; 50:10-23.
11. Gardner MJ, Montague TJ, Armstrong CS, Horacek BM, Smith ER. Vulnerability to ventricular arrhythmia: assessment by mapping of body surface potential. Circulation 1986; 73:684-92.