

4. Rationale:

The electrocardiogram (ECG) repolarization index Tpeak-Tend (Tp-Te) interval is gaining attention for its use in evaluating repolarization features in the myocardium (1). The peak of the T wave (Tp), i.e., the occurrence of the largest transmural gradient between the epicardium and endocardium, typically indicates that the epicardial aspect has just reached full repolarization. The end of the T wave (Te) is aligned with the end of the midmyocardial action potential, the total conclusion of repolarization. Canine and swine heart studies have demonstrated that the interval from Tp-Te is a marker of total dispersion in the heart and not just transmural dispersion (2, 3). Therefore, Tp-Te was suggested as an estimate of the total dispersion of repolarization providing clinical information of arrhythmic risk (4, 5) A case-control study reported that sudden cardiac death cases were significantly more likely to have prolonged Tp-Te interval measured in lead V5 compared to controls drawn from the same geographic area who had coronary artery disease (6) . Research on the association between the Tp-Te interval and health outcomes in population-based settings is quite limited, although work on the ability of Tp-Te and other measures of repolarization to predict incident CHD and mortality is currently underway in ARIC (ARIC Ms#1760).

The increased interest in the Tp-Te interval and its association with ventricular arrhythmia and sudden cardiac death makes it pertinent to evaluate the reproducibility of this measure. To our knowledge no such reproducibility study has been conducted.

We will evaluate the reproducibility of the Tp-Te interval data from the ARIC ancillary study identified as the ECG Repeatability Study (ReECG) (AS #2002.5), supplemented with the novel repolarization indices used in M#1760, provided by EPICARE. The aim of our study is to characterize the reproducibility and main sources of variability of the Tp-Te interval estimated from 6 repeat ECG measurements obtained under standardized conditions at the two examination visits in the ReECG Study.

5. Main Hypothesis/Study Questions:

1. Estimate the short-term reproducibility of the Tp-Te interval
2. Estimate the minimal detectable difference/change in the Tp-Te interval for use in observational studies

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 methodological limitations or challenges if present).

Measurements: Tp-Te interval and other repolarization measures were made using temporal reference points from the global T wave, and a spatial T vector magnitude from a transformation matrix.

Study design: Short-term reproducibility analysis of the Tp-Te interval will be conducted using repeated ECG data obtained under standardized conditions on 63 healthy, middle-aged volunteers at two examination visits conducted at the General Clinical Research Center at UNC Hospitals. Lead placements, the ECG equipment and the data acquisition protocol followed the ARIC ECG protocol. Prior to each morning's clinic visit, participants were advised to avoid smoking, eating and drinking all beverages other than water. Six ECG measurements were taken per participant: 3 at the initial visit (ECG1, ECG2, ECG3) and three one week later (ECG4, ECG5, ECG6). Four technicians were trained and certified by EPICARE personnel. Data were processed centrally at the Epidemiology Cardiology Research (EPICARE) Center, Wake Forest University, at Winston-Salem, NC.

Inclusions: Sixty-three apparently healthy participants from the ARIC ReECG ancillary study between the ages of 45-64.

Exclusions: Volunteers were excluded if using Ia antiarrhythmics, or having conditions such as an artificial pacemaker, renal failure, congestive heart failure, diabetes mellitus, and pregnant.

Outcome: Short-term reproducibility of the ECGs Tp-Te interval measured as the distance from the peak to the end of the T wave. The estimates of repeatability include the average difference within visit, between visits, the coefficient of variation and the intra-class correlation coefficient.

Statistical Analysis:

Summary measures: We will calculate the means and standard deviations (SD) for the measurements of the Tp-Te interval.

Coefficient of variation: The measure of the repeatability of Tp-Te interval across visits will be the coefficient of variation calculated as the within person SD divided by the mean. The lower the value is towards zero the more consistent the measures are over visits.

Intra-class correlation coefficient (ICC): This measure of the reproducibility of the Tp-Te interval will be calculated as the ratio of the between person variance over the total variance observed. High values indicate that most measurement variation is due to differences between participants and little due to other sources of error.

We will use a nested random-effects analysis of variance model to calculate the between subject, between visit and within visit variability of the Tp-Te measurement.

1. The average difference within visit: $[(\text{ECG 2}-\text{ECG1})+(\text{ECG5}-\text{ECG4})]/2$
2. The average difference between visit: $[(\text{ECG 4}-\text{ECG1})+(\text{ECG5}-\text{ECG2})]/2$
3. The absolute difference between measurements (ECG 2-ECG1, ECG5-ECG2)

Graphical displays of the difference between measurements to show the variability across the range of values will be made using Bland-Altman plots. We will calculate the minimal detectable change (MDC) to estimate the minimum change between two time points for an individual that reflects true change above that of measurement error.

Sensitivity analysis: We will conduct a sensitivity analysis to investigate whether excluding participants who did not comply with the ECG protocol and/or participants on pharmacologic therapies including β -blockers, cardiac glycosides, calcium-channel blockers, and antiarrhythmics affects the repeatability estimates.

Limitations:

The relatively small sample size is a limitation especially if there are outliers influencing the total variance. Our study includes standardized measurements of ECG conducted only at two points close in time, limiting our study to the estimation of short-term repeatability.

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)?

The most related manuscripts are based on ECG measures from the ECG Repeatability Study.

Manuscript Proposal # 2000 (Meyer M and collaborators) Short-term repeatability of electrocardiographic P wave indices and PR interval (in progress)

Manuscript Proposal # 894 Repeatability of Heart Rate Variability Measures: The ECG Repeatability Study (Published)

5. Castro Hevia J, Antzelevitch C, Tornes Barzaga F, et al. Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. *J Am Coll Cardiol.* 2006;47(9):1828-34. (doi: 10.1016/j.jacc.2005.12.049).
6. Panikkath R, Reinier K, Uy-Evanado A, et al. Prolonged Tpeak-to-tend interval on the resting ECG is associated with increased risk of sudden cardiac death. *Circ Arrhythm Electrophysiol.* 2011;4(4):441-7. (doi: 10.1161/CIRCEP.110.960658).