ARIC Manuscript Proposal #2000

PC Reviewed: 9/11/12  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Short-term repeatability of electrocardiographic P wave indices and PR interval

b. Abbreviated Title (Length 26 characters): Reproducibility of P wave

2. Writing Group:
   Writing group members: Michelle Meyer, Elsayed Z Soliman, Eric A Whitsel, Kapuaola Gellert, Gerardo Heiss, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _MM_ [please confirm with your initials electronically or in writing]

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3. Timeline: Analysis is to start as soon as approval is obtained. We plan to complete the
manuscript within one year from data analysis.

4. **Rationale:**

P wave indices and PR interval duration from standard 12-lead surface electrocardiograms (ECG) are simple measures of atrial electrophysiology and represent the entire process of atrial depolarization. The most commonly used indices are, maximum p wave duration, p-wave terminal force in V1, and p wave dispersion. Prolonged maximum p wave duration indicates a disturbance in conduction between the left and right atrium\(^1\) and increased p wave dispersion is believed to reflect heterogeneous conduction patterns of atrial impulses between the left and right atrium.\(^2\) Abnormal P-wave indices and prolonged PR interval are considered to be intermediate phenotypes of atrial fibrillation (AF) and predict the risk of AF.\(^2-4\) Recently, novel indices including p wave area has gained attention and is also predictive of AF.\(^5,6\)

Despite the common use of p wave indices and PR interval, their reproducibility has not been thoroughly examined. It is important to accurately assess the reproducibility of p wave indices since it is critical to the analysis and interpretation of these measures. One study assessed reproducibility of p wave indices using the intraclass correlation coefficient (ICC) and showed the intraobserver ICC for maximum p wave duration was 0.80 and the ICC for p wave dispersion was 0.82.\(^7\) The interobserver ICC for p wave maximum was 0.56 and the ICC for p wave dispersion was 0.70. However, a single lead acquisition method was used, which is less accurate than a simultaneous lead acquisition method with digital ECGs.

The Atherosclerosis Risk in Communities (ARIC) ancillary study identified as the ECG Repeatability Study (ReECG) (AS #2002.5) will allow us to evaluate the repeatability of p wave indices estimated from short term ECG readings in the ReECG Study. Defining the repeatability of p wave indices and PR interval would guide the interpretation and reporting of these measures.

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

1. Examine the repeatability of p wave indices and PR interval.
2. Estimate the minimal detectable change in p wave indices and PR interval for use in epidemiological studies.
3. Examine the use of repeated measurements for detecting changes in p wave indices and PR interval in a theoretical clinical trial.

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).**

**Study design:** Repeatability analysis of p wave indices from the ReECG Study. The ReECG study included 63 healthy participants 45-64 years old recruited from Chapel Hill, NC, that had similar characteristics to the ARIC study cohort at baseline with respect to age, gender and race.
Each participant underwent two visits at the General Clinical Research Center at UNC hospitals between July and October 2001. Three standard 12-lead ECG recordings were taken after participants rested for 15 minutes in the supine position at the initial visit (ECG1, ECG2, ECG3) and then one to two weeks later (ECG4, ECG5, ECG6). The ECG recordings were obtained by four trained technicians that followed the ECG protocol used in ARIC. The ECG recordings were taken using Kendall QT 5400 Ag/AgCl electrodes (Ludlow Co., Chicopee, MA) and digitized using the MAC PC Personal Cardiograph (Marquette Electronics, Inc., Jupiter, FL). The images were sent to the Epidemiology Cardiology Research (EPICARE) Center in Winston-Salem, NC, and were coded and processed using the Marquette GE program to generate the P wave indices.

Outcome: Repeatability estimates of P wave indices.

P wave indices for the analysis include:
1. P wave duration (ms) - maximum
   a. Lead-specific P wave duration = P duration in lead * + P' duration in lead *, where * in (AVF, AVL, AVR, I, II, III, V1, V2, V3, V4, V5, V6)
2. P wave dispersion (ms) - maximum-minimum P wave duration
   a. Zero values will be excluded when determining the minimum duration.
3. P wave area (μV*ms) - maximum
   a. Lead-specific P wave area = P area in lead * + P' area in lead *, where * in (AVF, AVL, AVR, I, II, III, V1, V2, V3, V4, V5, V6)
4. P wave terminal force (μV*ms) - at lead V1
   a. P' duration in lead V1 multiplied by the P' amplitude in lead V1
5. PR interval duration (ms) and HR-adjusted PR interval duration (PRa) (ms)
   a. Adjusted for heart rate using Soliman and Rautharju method8 where heart rate–adjusted PR interval (PRa) is calculated using the formula PRa = PR + 0.26 (HR – 70) for age < 60 years and PRa = PR + 0.42 (HR – 70) for age 60 years or older.

Inclusions: The 63 participants from the ReECG ancillary study.

Exclusions: Participants lacking ECGs or unreadable ECGs.

Statistical Analysis:

We will present p indices and PR interval for each ECG measurement as means and standard deviations (SD). P indices with a skewed distribution will be expressed as medians and interquartile ranges and will be log transformed for the analysis.

We will also calculate:
1. The average difference within visit: [(ECG 2-ECG1)+ (ECG3-ECG1) +(ECG 5-ECG4) + (ECG 6-ECG4)]/4
2. The average difference between visit: [(ECG 4-ECG1)+ (ECG5-ECG2) +(ECG 6-ECG3)]/3
3. The absolute difference between measurements (ECG 2-ECG1, ECG3-ECG1 and ECG 5-ECG4, ECG6-ECG4) and display histograms of the results.

A nested random-effects analysis of variance model will be used to estimate the between-participant, between-visit and within-visit variance. We will calculate the intra-class correlation coefficient (ICC) by dividing the between-participant variance by the total variance to estimate the reproducibility of the indices.

Bland-Altman plots will be used to visually display the difference between measurements against their mean to see if the variability is equal across the range of values.

We will calculate reference change values (RCV) for p indices to estimate the percent change threshold in serial measures that is greater than the percent change expected due to biological variation and measurement error. In addition 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.

To examine the use of repeated measurements in a theoretical clinical trial for detecting changes in p wave indices and PR interval, the 95% confidence limits will be estimated for changes in p indices and PR interval based on the number of measurements and sample size.

Sensitivity analyses: In a sensitivity analyses, we will 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:
ECG measurements are available at only two time points (initial visit and 1 week later) thus our analysis is limited to short term repeatability. Also, the study included non-ARIC participants but they were selected to be similar to the ARIC Cohort.

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.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)?

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

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

Manuscript Proposal # 897 Repeatability of the Spatial T Wave Axis Deviation Measures: The ECG Repeatability Study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes    _____ No

11.b. If yes, is the proposal

__X__ A. primarily the result of an ancillary study (list number* __AS #2002.05__)

_____ 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/

This study will use ECG data obtained from the ancillary study: AS #2002.5 ECG Repeatability Study (ReECG) Heiss, G

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


