ARIC Manuscript Proposal #2665

PC Reviewed: 11/10/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:

Repeatability of ectopic beats from 48 hour ambulatory electrocardiography: The ARIC study

b. Abbreviated Title (Length 26 characters):
Repeatability of ectopic beats

2. Writing Group:
Writing group members:

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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: Final data collection should be complete by March 2016. Manuscript fully drafted in to the ARIC publications committee by May/June 2016. We also plan to submit an abstract to the AHA Epidemiology meeting due in Oct, 2015.

4. Rationale:

Atrial fibrillation (AF), the most common sustained arrhythmia worldwide, is an emerging public health issue given the increasing prevalence and the associated morbidity and health care costs.[1] Premature atrial and ventricular ectopic beats (premature atrial contractions (PACs) and premature ventricular contractions (PVCs), respectively) are common arrhythmias that often precede AF and may indicate paroxysmal AF. Recent evidence suggests that PACs are associated with the development of AF and may be a predictor of stroke.[2-4] Excessive number of PACs from ambulatory electrocardiography (ECG) monitoring are associated with AF, stroke and death in participants with AF-like symptoms[5] and in population-based studies.[2, 6-8]

Most prior studies used 24- to 48-hour ambulatory ECG monitoring, but did not report the repeatability of PACs and PVCs, which would provide critical information about measurement variability and have implications for interpreting results. Furthermore, the effect of the length of ambulatory ECG monitoring on the repeatability of PACs and PVCs has not been investigated. The aim of this study is to evaluate the reproducibility of PACs and PVCs in 48-hour ambulatory ECG monitoring, and evaluate the length of ECG monitoring on the repeatability estimates among a biethnic population of older adults in the ARIC 48-hour ambulatory ECG study.

5. Main Hypothesis/Study Questions:

1. Quantify the repeatability of PACs and PVCs.
2. Examine the effect of the length of Holter monitoring on repeatability estimates for PACs and PVCs.

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 methodologic limitations or challenges if present).

Study design:

This repeatability analysis will include a subset of ARIC Visit 5 participants that were selected for a 48-hour ambulatory electrocardiography ancillary study and invited to participate in the repeatability study. The ancillary study took place at two ARIC sites: Forsyth County, NC, and Jackson, MS. For the repeatability study, 100 participants (50 from each study site) were randomly selected to wear the Holter monitor for an additional 48 hours. Those selected returned to the clinic within the next month to have the monitor replaced. The target for the volunteer sample was ~50 women and ~60% African Americans (all 50 participants from Jackson are African American). The repeat visit had the same incentive ($50 + $15 if monitor promptly returned) as offered for the first visit.

The protocol for the repeat study visit was the same as the first study visit. The study visit included placement of the Holter monitor, education on wearing the monitor, and start of the recording. Participants received a new monitor, new batteries, and new

electrodes. The device was connected at the examination center and the quality of signal confirmed. After the completion of the monitoring period, participants were asked to fill out a post-visit questionnaire regarding symptoms or problems while wearing the monitor. EPICARE processed the repeated measures using the same standardized protocol as the first visit, and were blinded to the fact that they were repeats and blinded to the values from the first visit.

Outcome: Repeatability estimates of supraventricular ectopic beats (PACs) and ventricular ectopic beats (PVCs).

The following measures will be defined separately for PACs and PVCs:

- Log of the total number of PACs, Log of the total number of PVCs
- Percentage of counts: total number of ectopic beats divided by the total number of beats recorded during the length of Holter monitoring x 100
  - % PACs = (number of PACs / number of QRS complexes) x 100
  - % PVCs = (number of PVCs / number of QRS complexes) x 100
- Quartiles and distribution-based cut-point based on the upper 20^{th} percentile of the total counts

Other variables: Time between recordings, field center, age, gender, race, history of coronary artery disease, sleep apnea, heart rate, systolic blood pressure, body mass index, smoking status, and use of antiarrhythmic or vasoactive medications.

Inclusions: All participants that attended the AF study and wore a Holter monitor and also underwent a repeat visit.

Exclusions: Participants with poor quality measures, defined as noise >10%. We will exclude participants with AF and those with frequent paced beats.

Statistical Analysis:

We will present the median and interquartile range for the number of PACs and PVCs during each recording period (visit 1 and visit 2). Descriptive statistics will be used to characterize the number of PACs and PVCs over the duration of monitoring. The average and absolute difference between pairs of measurements between-visits will be calculated (visit 2 minus visit 1).

Bland-Altman plots will be used to examine agreement between visits for the number of PACs and PVCs. The Kappa (K) and weighted Kappa (K_w) will be used to evaluate agreement between-visits for the upper 20^{th} percentile cut-point and quartiles (defined consistently between visits) of PACs and PVCs. Linear, Cicchetti-Allison weights (w) will be used for the quartiles [$K_w = P_{o(w)} - P_{e(w)}/1\text{-}P_{e(w)}$].

To examine within-visit repeatability, each 48-hour recording will be split into two 24-hour recordings. Nested random-effects analysis of variance models will be used to estimate the between-participant (σ^2_p), between-visit (σ^2_{bv}), and within-visit (σ^2_{wv}) variation. The model is defined as the following: $Y_{ijk}=\mu + P_i + V_{j(i)} = e_{k(ij)}$ where Y = log of the PAC or PVC count, μ = the intercept, i = 1,2,3 to the 86^{th} participant, j =visit one or visit two, and k = the first or second measurement (i.e. 24-hour recording). PACs and

PVCs will be log transformed for the analysis due to an expected skewed distribution. Our assumptions are that the between-visit variation is the same for all participants and the within-visit variation is the same for all visits and all participants, as previously described in the ECG repeatability analyses (ARIC MS# 894, 897, 2000, 2012).

To estimate the repeatability of PACs and PVCs, the intraclass correlation coefficient (ICC) was calculated by dividing the between-participant variance by the total variance [$\sigma^2_p/\sigma^2_{total} = \sigma^2_p/(\sigma^2_p+\sigma^2_{bv}+\sigma^2_{wv})$]. Measures will be log transformed to compute the ICC since the confidence interval is sensitive to departures from normality. We also will calculate the standard error of measurement (SEM) that represents the amount of measurement error, or repeatability, within an individual [$SEM = \sqrt{(\sigma^2_{bv}+\sigma^2_{wv})}$]. Additionally, we will evaluate the effect different length of recordings on repeatability by considering only the first 2-hours, 6-hours, and 12-hours of monitoring for each 24-hour recording.

Sensitivity analysis: In a sensitivity analysis, we will investigate whether excluding participants who reported current smoking or the use of antiarrhythmic or vasoactive medications affects the repeatability estimates. We will also conduct a sensitivity analysis restricted to participants with repeat visits within the 30-day time period originally specified.

Limitations: Holter measurements are available at only two time points, thus our analysis is limited to short-term repeatability for two visits. Although the visits were conducted back to back using a standardized protocol and study procedures designed to minimize measurement variability, it is possible that conditions were not exactly the same.

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 ICTDER 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)? There are no closely related manuscripts, however this one includes long-term monitoring: #2273a Ultra-low frequency heart rate variability on 14-day ECG and cognitive function. Multiple co-authors have been included in this project.

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* 2012.08)

___ 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/

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.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __x__ No.

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