ARIC Manuscript Proposal # 3295

1.a. **Full Title:** Increasing Tachycardic Asymmetry in Heart Rate Variability is Associated with Sudden Cardiac Death in the Community: The Atherosclerosis Risk in Communities (ARIC) study

b. **Abbreviated Title (Length 26 characters):** Porta HRV index and SCD

2. **Writing Group:**

Writing group members:
- Aron Bender, MD, (design, background literature review, interpretation of results, writing)
- Muammar Kabir, PhD, (Matlab software development and automated ECG analyses, interpretation of results)
- David German, MD, Tuan Mai, MD, Srini V. Mukundan, MD, (clinical adjudication of each cardiac beat origin and conduction path = beats labeling, interpretation of results)
- Christopher Hamilton, BA, Jason Thomas, BS (quality control of ECG analyses, review of accuracy fiducial points, interpretation of results)
- Larisa G. Tereshchenko, MD, PhD (design, beats labeling, statistical analyses, oversight, interpretation of results, writing)

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

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**ARIC author** to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
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3. **Timeline:** 2019

4. **Rationale:**

Abnormal decreased heart rate variability (HRV) is associated with increased risk of all-cause mortality, cardiovascular mortality, and sudden cardiac death (SCD), implicating involvement of the autonomic nervous system. Unfortunately, decreased HRV is a non-specific predictor of
cardiovascular events. Several non-linear HRV indices have been developed with the goal to improve specificity of HRV. One of such non-linear HRV measures is the Porta index. Porta index measures time asymmetry in HRV, corresponding to disproportionate relative tachycardic predominance.\(^1\) An association between SCD and Porta index has not previously been studied.

5. **Main Hypothesis/Study Questions:**
We hypothesized that increasing tachycardic asymmetry as measured by Porta’s Index is associated with SCD.

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).**

ARIC participants with available and analyzable ECGs in sinus rhythm will be included. We will exclude Black participants in the Washington and Minnesota cohorts and participants with reported race other than white or black, and participants with missing covariates. Participants with atrial fibrillation, premature contractions, sinoatrial (SA) or atrioventricular (AV) blocks II-III will be excluded.

Custom Matlab software was developed for analysis. Only normal sinus beats were included in the semi-automated analysis. The accuracy of automated R-peak detection was manually validated. Porta index is calculated as the percentage of points below the identity line with respect to the total number of points outside the identity line.

We will conduct survival analysis, using Cox and competing risk regressions. SCD is the primary outcome. Non-SCD, and non-cardiac death served as competing outcomes in a Fine and Gray competing risk model.

We will construct several models with the goal to determine whether association of the Porta index with SCD is independent from structural heart disease (CVD and its risk factors). Model 1 is adjusted for demographic characteristics (age, sex, race, and study center). Model 2 is in addition adjusted for prevalent CVD and its risk factors (CHD, HF, stroke, use of β-blockers, creatinine, body mass index, hypertension, antihypertensive medications, diabetes mellitus, smoking status, alcohol intake, total cholesterol, high density lipoprotein cholesterol, triglycerides, and physical activity index). Model 3 further adjusted for electrocardiographic parameters associated with SCD (heart rate, PR interval, QRS, QTc duration, sex-specific Cornell product, and bundle-branch block, or intraventricular conduction delay). Model 4 evaluated whether the association of GEH parameters remained significant over time and included all baseline covariates included in model 3, time-updated GEH parameters, time-updated traditional electrocardiographic measurements, and time-updated incident nonfatal cardiovascular events (AF, HF, CHD, and stroke). Schoenfeld residuals will be used to confirm that the proportional hazards assumption is valid in all Cox proportional hazards models.

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
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/mantrack/maintain/search/dtSearch.html

  _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)?  2208

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* _2012.14___)

  ___  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 https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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: