1.a. Full Title: Longitudinal association of global electrical heterogeneity with physical activity: The Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters): GEH and physical activity

2. Writing Group:
   Writing group members:
   - Nichole Rogovoy, BS, (background literature review, interpretation of results, writing)
   - Erick A. Perez-Alday, PhD, Yin Li-Pershing, BS (Matlab software development and automated ECG analyses, interpretation of results)
   - Aron Bender, MD, 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 (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. NR 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:
   We recently showed that electrocardiographic global electrical heterogeneity (ECG-GEH), measured by five features of the spatial ventricular gradient (SVG) vector (SVG magnitude, direction (azimuth and elevation), its scalar value [sum absolute QRST integral (SAI QRST)],
and spatial QRS-T angle) on orthogonal XYZ ECG is associated with sudden cardiac death (SCD). In the pooled ARIC+CHS population,1 we showed that 5 GEH measurements were independently associated with SCD after adjustment for demographics, manifested CV disease (time-updated incident non-fatal cardiovascular events [CHD, HF, stroke, AF, use of beta-blockers], and known CV risk factors such as total cholesterol, HDL, triglycerides, physical activity index, smoking, diabetes, BMI, hypertension, anti-hypertensive medications, creatinine, alcohol intake, LVEF, and time-updated ECG risk-factors. GEH selectively predicted SCD over non-sudden fatal CHD and non-cardiac death in competing risks models, suggesting that abnormal GEH selectively identified participants with abnormal EP substrate rather than simply identifying a sicker population with structural heart disease.

In another our study of young alpine skiers2, we observed ECG-right ventricular hypertrophy (RVH) in nearly one in five athletes. We observed2 an association of athletic performance, but not athletic training, with spatial QRS-T angle. Higher athletic performance in the downhill discipline was associated with narrower QRS-T angle. It remains unknown whether transient myocardial injury can lead to a chronic myocardial damage and clinical events, and it is unknown how to identify athletes at risk.3 Our proposed study can make one step towards answering this question. Signaling pathways and molecular mechanisms responsible for mediating pathological vs. physiological cardiac hypertrophy induced by long-term exercise training are different.4 The insulin-like growth factor 1 (IGF1) signaling pathway regulates exercise-induced physiological cardiac hypertrophy and cardiac protection.4

Our GEH GWAS identified a GEH-associated genetic polymorphism in the intron of the IGF1-Receptor (IGF1R) gene.5 As demonstrated by an IGF1R locus-associated GEH phenotype (Figure 4E in5), physiological cardiac remodeling in the athlete’s heart is characterized by sizable increase in SAI QRST and SVG magnitude with only mild increase in SVG azimuth and QRS-T angle, and simultaneous decrease in SVG elevation. Thus, GEH presentation can potentially distinguish athletes with physiological RV remodeling from those who are over-trained and are at risk to develop RV dysfunction.

We designed this study to investigate longitudinal (possibly causative) associations between physical activity and GEH phenotype.

5. Main Hypothesis/Study Questions:
We hypothesize that physical activity is associated with GEH phenotype in longitudinal analysis.

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).

All ARIC participants with available and analyzable ECGs, who have GEH results reported (both area vectors1 and peak vectors6) will be included. We will exclude participants without physical activity data, participants with race other than black or white, and black participants in MN and Washington county (MD).

Mixed regression models7 will be used. In order to determine whether the patient-specific time-varying changes in the physical activity level are associated with the patient-specific time-varying GEH changes, we will conduct generalized least squares random-effects linear regression analysis. First, patient-specific time-varying ECG variables (continuous variables, each in separate models set) will serve as an outcome. Patient-specific time-varying physical
activity level will serve as a predictor. We will perform Hausman test to choose between the random-effect estimator (assuming that the unobserved time-invariant random component is unrelated to the predictors) and fixed-effect estimator (allowing the unobserved random component to be related to the predictors). We will adjust for confounding demographic variables and known CVD risk factors. Longitudinal analyses will be conducted in a structural equation modeling framework. Physical activity measured at visit 1 will serve as predictor of GEH at visit 2. Physical activity measured at visit 2 will serve as a predictor of GEH at visit 3. There will be no cross-sectional associations included; longitudinal only.

Next, to assess reverse causality, GEH variables will serve as predictor, and physical activity level - as an outcome. We hypothesize that GEH does not predict physical activity level. Circular statistics will be used to study circular variables (SVG azimuth and elevation).

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/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:


