1.a. Full Title: Longitudinal association of global electrical heterogeneity with anthropometric characteristics and obesity: The Atherosclerosis Risk in Communities (ARIC) study

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

2. Writing Group:
   Writing group members:
   - Nichole Rogovoy, BS, (background literature review, interpretation of results, writing, design)
   - 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, 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.

It is well-known that ECG characteristics are associated with anthropometric characteristics: height, weight, and body mass index (BMI). It is unknown which anthropometric characteristics (waist-to-hip ratio, BMI, body surface area (BSA), height, weight) have the strongest/weakest association with GEH in cross-sectional analysis. Our study will address this knowledge gap. Also, as we have available longitudinal anthropometric measurements, and GEH measurements at every study visit, we will be able to assess longitudinal associations between these two phenotypes. We hypothesize that longitudinal changes in body mass index (BMI), body surface area (BSA) are associated with longitudinal changes in GEH phenotype. Our study will provide us an opportunity to test our analytical strategy. We can hypothesize that anthropometrics can exert causative effect on GEH metrics, but reverse causality would be impossible to imagine, as GEH cannot “cause” BMI/BSA changes. We will test these hypotheses in our study.

5. Main Hypothesis/Study Questions:
We hypothesize that BMI (and other anthropometrics) is associated with GEH phenotype in cross-sectional and longitudinal analyses.

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 vectors and peak vectors) 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).

For cross-sectional analysis, Multiple linear regressions will be constructed to test cross-sectional associations between predictor variables, one-by-one (BMI, BSA, height, weight, waist-to-hip ratio) and GEH variables as outcomes (one-by-one). P-value will be adjusted per Bonferroni correction, to account for multiple testing. Linear regression models will be adjusted for sex, race, and study center, and prevalent CVD and its risk factors.

For longitudinal analysis, Mixed regression models will be used. In order to determine whether the patient-specific time-varying changes in the BMI (and other anthropometric variables, one by one)-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 BMI 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. BMI measured at visit 1 will serve as predictor of GEH at visit 2. BMI 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 BMI (and other anthropometric variables one by one)- as an outcome. We hypothesize that GEH does not predict anthropometrics.

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 ___X__ 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 ___X__ 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:


