ARIC Manuscript Proposal # 3047

PC Reviewed: 9/12/17   **Status: _____**   **Priority: 2**
SC Reviewed: _____   **Status: _____**   **Priority: ____**

1.a. Full Title: Insulin resistance indexes and heart rate variability in older adults: the Atherosclerosis Risk in Communities Study (ARIC)

  b. Abbreviated Title (Length 26 characters): IR indexes and HRV

2.   Writing Group:
    Writing group members: Anna K Poon, Laura Loehr, Eric Whitsel, Gerardo Heiss, Elsayed Soliman, Lynne Wagenknecht, Takeki Suzuki, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. AKP **[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: This manuscript will be completed one year after manuscript approval.

4.   Rationale:

Heart rate variability is a non-invasive measure of cardiac autonomic function. It is based on an analysis of the intervals between successive normal complexes (NN intervals). In time domain analyses, common parameters include the standard deviation of all NN intervals (SDNN) and the square root of the mean squared differences of successive NN intervals (RMSSD). In frequency domain analyses, common parameters include the low-frequency spectral component (LF) and high-frequency spectral component (HF) (1996, Hillebrand et al., 2013). Changes in these heart rate variability metrics signify changes in sympathetic and parasympathetic activity.

Lower heart rate variability leads to cardiovascular disease and cardiovascular disease-related mortality in diabetes. In a prospective study of adults with 2-minute monitoring, lower heart rate variability was associated with increased risk of coronary heart disease events in individuals with diabetes (n=1275), but not in individuals without diabetes (n=10379) (Liao et al., 2002). In a prospective study of adults with 1-minute and 3-minute monitoring, lower heart rate variability was consistently, but not statistically significantly, associated with increased risk of cardiovascular mortality in those with diabetes (n=159), but not in those without diabetes (n=446) (Gerritsen et al., 2001). Whether insulin resistance contributes to heart rate variability early on, prior to diabetes (i.e., in the absence of diabetes), remains to be determined.

Indeed, evidence on the relationship between insulin resistance and heart rate variability is not clear in population-based studies. In a cross-sectional study of adults 45-64 years of age with 2- and 6- minute monitoring (n=8,971), lower heart rate variability was associated with higher insulin levels and weakly associated with higher glucose levels (Schroeder et al., 2005). In a cross-sectional study of adults 30-79 years of age with 5-minute monitoring (n=1899), higher insulin resistance indexes was associated with lower heart rate variability (Saito et al., 2015). In a separate cross-sectional study of adults 23-70 years of age with 5-minute monitoring (n=220), although the presence of the metabolic syndrome was associated with lower heart rate variability, higher insulin resistance indexes was not associated with lower heart rate variability (Stuckey et al., 2015). The inferences differ across studies.

These prior studies raise questions. The differences observed in these studies may be attributable in part to the length of electrocardiographic monitoring; longer monitoring length may reduce measurement error (Schroeder et al., 2005). The differences may also be attributable in part to the assessment of insulin resistance levels; in addition to the use of glucose and insulin based indexes, the use of lipid based indexes may reduce measurement error. Moreover, no prior studies have examined this relationship in older adults; the relationship between insulin resistance and heart rate variability may change with age.

To address these differences, our goal is to understand the relationship between insulin resistance indexes and heart rate variability in a community-based population of older adults with 48-hour monitoring.

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

- **Aim:** To determine the association of insulin resistance indexes with heart rate variability.
- **Hypothesis #1:** Higher insulin resistance indexes will be associated with lower heart rate variability.
- **Hypothesis #2:** This association -- defined by the difference in heart rate variability per unit difference in insulin resistance index -- will be stronger in women than men.
- **Hypothesis #3:** This association -- defined by the difference in heart rate variability per unit difference in insulin resistance index -- will not differ between African American participants and white participants.
- **Hypothesis #4:** This association -- defined by the difference in heart rate variability per unit difference in insulin resistance index -- will be stronger in those with, compared to those without, hypertension.

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: The study participants will include participants who attended Visit 5 and participated in the 48-hour Holter monitoring ancillary study visit.

Exclusions: Exclusions will include: 1) diabetes at visit 5 or at the ancillary study visit; and 2) use of antiarrhythmic medications.

Outcome: Outcomes will include heart rate variability defined by SDNN, RMSSD, HF, and LF. The equation for SDNN is: $SDNN = \sqrt{\frac{\sum_{i=1}^{n}(NN_i - NN_{mean})^2}{n-1}}$. The equation for RMSSD is: $RMSSD = \sqrt{\frac{\sum_{i=1}^{n-1}(NN_{i+1} - NN_i)^2}{n}}$. For both SDNN and RMSSD, n = the total number of NN intervals over the ECG duration.

Exposure: Exposures will include insulin resistance indexes defined by the homeostatic model assessment of insulin resistance (HOMA-IR), the triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C), and the triglyceride glucose index (TyG). The equation for HOMA-IR is: HOMA-IR = (fasting glucose in mg/dL) x (insulin in μU/mL) / 405. The equation for TG/HDL-C is: TG/HDL-C = (triglyceride in mg/dL) / (high-density lipoprotein cholesterol in mg/dL). The equation for TyG is: TyG = ln(fasting triglyceride in mg/dL) x (fasting glucose in mg/dL) / 2.

Covariates: Covariates include age, gender, race, study center, waist circumference, systolic blood pressure, diastolic blood pressure, hypertension status, heart rate, and blood pressure lowering medications. Other covariates include: family history of diabetes, physical activity, diet, and alcohol consumption.

Statistical Analysis: We will examine the distribution of the heart rate variability parameters using histograms and descriptive statistics. We will examine the relationship between the heart rate variability parameters (the outcome) with each insulin resistance index (the exposure) using scatter plots and descriptive statistics; we will examine heterogeneity by gender, race, and hypertension status. We will determine the difference in heart rate variability per unit difference in insulin resistance index using linear regression. We will determine the interaction, if any: 1) between insulin resistance index and gender; 2) between insulin resistance index and race; and 3) between insulin resistance index and hypertension status.

Additional Analysis: Exclude for beta-blockers.

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 ____ 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)?

A prior study was conducted examining the relationship between diabetes, glucose, insulin, and heart rate variability, entitled "Diabetes, glucose, insulin, and heart rate variability: the Atherosclerosis Risk in Communities (ARIC) Study" by Schroeder et al. (2005).

Our study contributes to this prior study in three aspects. First, the study population includes adults ~66-90 years of age; the prior study included adults 45-64 years of age. Our study examines the relationship between insulin resistance and heart rate variability in late-life, as opposed to mid-life, which may provide different inferences given the relationship between age and insulin resistance.

Second, the proposed study assesses insulin resistance levels with composite, as opposed to separate, measures that reflect different aspects of insulin resistance. The HOMA-IR reflects the dysregulation of insulin and glucose, whereas the TG/HDL-C reflects the dyslipidemia seen in insulin resistance. The repeatability of these composite measures address potential issues with measurement error and regression dilution bias; the short-term repeatability is good to fair for HOMA-IR (ICC 0.70) and excellent for TG/HDL-C (ICC 0.80) according to suggested benchmarks.

Third, the proposed study assesses heart rate variability by examining both time domain analyses and, in addition, frequency domain analyses assessed over a 48-hour period. These heart rate variability measurements reflect sympathetic and parasympathetic nervous system activity: SDNN represents sympathetic and parasympathetic activity; RMSSD represents parasympathetic activity; HF represents parasympathetic activity; and LF represents sympathetic and parasympathetic tone. Due to the longer length of monitoring, the repeatability of these heart rate variability measurements address potential issues with measurement error. The short-term repeatability of 6-minute measurements are the following: SDNN (ICC 0.87); RMSSD (ICC 0.91); HF (ICC 0.85); and LF (ICC 0.83) (Schroeder et al., 2004).

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, approved manuscripts using 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.

References

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