ARIC Manuscript Proposal # 1611

PC Reviewed: 2/9/10	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
P Wave Indices' Association with Obesity and Metabolic Syndrome: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters):
P Wave Indices and Obesity

2. Writing Group:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _JWM____ **[please confirm with your initials electronically or in writing]**

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3. Timeline:

Assembly of preliminary data will be initiated immediately following proposal approval. Data cleaning and organization will occur over the subsequent 6 months. Analysis is anticipated to be completed in September 2010. Composition and submission of initial manuscript is anticipated by January 2011. Data analysis will be done at the University of Minnesota.

4. Rationale:

P wave indices describe atrial characteristics of amplitude and duration derived from the surface electrocardiogram (ECG). They include the P wave maximum and mean duration; the maximum and mean area; terminal force, the product of the negative phase amplitude in lead V1 and its duration; and the PR duration. As an intermediate phenotype, they reflect an array of ischemic, metabolic and hemodynamic influences which determine atrial electrophysiology and morphology.[1] Most investigation of P wave indices has focused on their utility for the assessment of risk of atrial fibrillation. Examples of the latter include paroxysmal AF,[2-4] recurrent AF following cardioversion,[5-7] AF following cardiothoracic surgery,[8-10] and predicting incident AF.[8] The largest identified study to date evaluating P wave indices occurred in the Atherosclerosis Risk in Communities (ARIC) study, and found significant associations between abnormal P wave indices with incident AF and stroke.[9]

P wave indices have similarly been assessed in cardiac risk factors, particularly diabetes and obesity. In a cross-sectional analysis of diabetic subjects, the P wave indices of duration and dispersion were significantly longer compared to a reference cohort.[10] In obese subjects, these measurements were longer compared to control groups, both with and without adjustment for clinical variables.[11, 12] Decreases in P wave duration and dispersion have been observed with weight loss[13] and following bariatric surgery in a morbidly obese cohort.[14]

These studies were selected cohorts, predominantly cross-sectional, with small sample sizes resulting in poor statistical power, and had limited inclusion and adjustment for relevant covariates. Nevertheless, they suggest components of the pathway from metabolic insult to atrial remodeling and fibrosis that are recognized hallmarks of AF.[15-17] Insulin resistance and obesity have been established as inflammatory states with pleiotropic effects that include hypertension, cardiovascular risk, thrombosis, and inflammation.[15, 18-22] Obesity is a chief risk factor for AF.[23] The association between obesity and AF is hypothesized to result primarily from the milieu of oxidative stress and inflammation secondary to the obese state.[24, 25]

P wave indices may therefore constitute an endophenotype which is prolonged by obesity and as such may constitute an intermediate marker along the pathway from the exposure of obesity to the outcome of AF. We propose to examine associations between P wave indices and components of obesity, including BMI and elements of the metabolic syndrome.[26-28] We hypothesize that (1) the P wave indices of duration, area, and terminal force are prolonged in obese compared to non-obese individuals; (2) that we will identify at least a moderate correlation between BMI and P wave indices; and that (3) individuals with progressively increased components of the metabolic syndrome will have correspondingly larger P wave indices.

These findings will contribute unique insights into the epidemiology of P wave indices. ARIC is a large, multiethnic cohort which has been well characterized and provides a unique opportunity for our study. The largest published study to date describing P wave indices comes from ARIC. We intend our results to guide further investigations examining the mechanisms between obesity and AF.

5. Main Hypothesis/Study Questions:

Primary hypothesis:
Obesity, as defined by BMI, and its surrogates, i.e. waist circumference, are associated with significantly increased P wave indices of duration, area, and terminal force, independently of other cardiovascular risk factors.

Secondary hypothesis 1:
Components of the metabolic syndrome are similarly associated with increased P wave indices.

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).

This study will consist of a cross-sectional analysis using ARIC visit 1. All data will be obtained from the baseline exam and ECG, previously employed to examine the association of P wave indices with the outcomes of AF and stroke in ARIC.[9]

Inclusion/exclusion:
Participants with missing ECGs or with ECG conditions that interfere with calculation of P-wave indices will be excluded (atrial fibrillation, advanced degree heart block, pacemaker, and WPW). We will also exclude the small number of participants who reported a race/ethnicity other than white or black. This will yield a study sample similar to that used in the prior ARIC P wave indices manuscript, 15,429 participants.
Variables of interest, including covariates and outcomes:

Clinical correlates (measured at baseline)
Age
Sex
Race/Ethnicity
Site
Socioeconomic status (education, income)
Body mass index
Waist circumference
Height
Cigarette smoking (current, past, never; cigarette-years of smoking)
Alcohol intake, moderate and heavy
Physical activity
Hypertension, use of antihypertensive medications
Use of AV nodal blocking agents (beta blockers; non-dihydropyridine calcium channel blockers; digitalis/digoxin; procainamide)

Diabetes
Ratio of Total to HDL cholesterol
Systolic blood pressure
Diastolic blood pressure
Metabolic syndrome (defined according standard AHA/NHLBI criteria: 3 or more of the following conditions, (1) waist circumference >=88 cm in women or >=102 in men, (2) fasting triglycerides >=150 mg/dL (or on lipid medication), (3) HDLc<50 mg/dL in women or <40 mg/dL in men, or on lipid medication, (4) blood pressure >=130/>=85 or history of treated hypertension, (5) fasting glucose >=100 mg/dL or history of diabetes or receiving diabetes medication).[29]
Prior myocardial infarction
Prior stroke
Prior heart failure

Electrocardiographic variables, including P wave indices (measured at baseline)

Heart rate
PR interval
P wave duration, (maximum, median)
P wave amplitude (maximum)
P wave area
P wave terminal force
P wave dispersion (maximum - minimum P wave duration)
QRS interval
Electrocardiographic LVH

Summary of data analysis:
We will examine the distribution of the demographic, clinical, anthropometric and dietary characteristics as well as P wave indices in all participants. We will stratify by cardiovascular disease (defined as history of MI, stroke, or heart failure). In both strata, P wave indices will be considered in their reported quantities and logarithmically transformed to normalize their distributions if skewed. The association between P wave indices and variables of interest will be examined graphically. Age-, sex-, and race-adjusted correlation coefficients will be estimated for the correlations of the P wave indices with each other.

Primary hypothesis: BMI and waist circumference are associated with P wave indices. For each strata, we will fit linear regression models with the different P wave indices as dependent variables. Graphical methods and restricted cubic splines will be used to determine the shape of the association between main independent variables and P wave indices. Depending on this analysis, BMI and waist circumference will be examined as a continuous variable and/or in categorical quantities.

In an initial model, we will adjust for age, gender, and race. In a second model we will add the following covariates: study site, education, income, height, smoking, alcohol intake, sports-related physical activity, systolic and diastolic blood pressure, heart rate, use of antihypertensive medication, diabetes, ratio of total to HDLc, use of lipid lowering medication, and for specific medications which may impact AV nodal conduction (beta blockers; non-dihydropyridine calcium channel blockers; digitalis/digoxin; procainamide).

Secondary hypothesis: metabolic syndrome is associated with P wave indices.

As with the primary hypothesis, we will run an initial linear model adjusting for age, sex, and race, with metabolic syndrome (yes/no) as the main independent variable, and P wave indices as the dependent variables. A second model will adjust for other variables (excluding metabolic syndrome components).

We will also run models with the number of metabolic syndrome components as the main exposure (categorical variable).

In secondary analyses we will examine for effect modification by age, sex and race, including interaction terms in the models and conducting stratified analyses.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes XXX 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 ICTDER03 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 XXX 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

XXX 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)?
MS #1156 ECG prediction of atrial fibrillation and its impact on understanding the ethnic distribution of stroke in the ARIC study (Soliman). MS 1156 (Stroke. 2009 ;40(4):1204-11) focused on P wave indices and the association with atrial fibrillation in ECG follow-ups and stroke incidence. The current proposal has a broader focus, including other cardiovascular outcomes in addition to stroke.

MS #1559 PR interval, P wave indices and the incidence of atrial fibrillation: the ARIC study (Alonso). MS1559 focuses specifically on the association of PR interval and P

wave indices with atrial fibrillation, while the current proposal focuses on other cardiovascular outcomes, mortality and clinical correlates of P wave indices.

MS #1584 Epidemiology of P wave indices: clinical associations and long-term outcomes. This proposal focus on the association of P wave indices with incidence of heart failure, cardiovascular disease, and all-cause mortality. Also, it will explore the association between P wave indices and some cardiovascular risk factors. The current proposal, in contrast, will specifically focus on obesity (BMI, waist circumference) and the metabolic syndrome.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? **____ Yes** XXX **No**

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

___ 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/

12. 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.

Reference List

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