1.a. Full Title:
Longitudinal correlates of P wave indices: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters):
Longitudinal P wave indices

2. Writing Group:
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Other authors with involvement in relevant data will be invited to participate.

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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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:**
- Assembly of preliminary data will be initiated immediately following proposal approval. Data organization will occur over the subsequent 6 months.
- Analysis will be completed by 4/2011.
- Composition and submission of initial manuscript is anticipated by 6/2011.

4. **Rationale:**

Atrial fibrillation (AF) has an estimated prevalence of 2.3 million people in the United States and is expected to increase to 6 to 12 million by 2050.\(^1\) The lifetime risk of developing AF has been determined as 23% in women and 26% in men in a community-based cohort of individuals over 40 years of age.\(^2\) AF increases stroke risk by 3-5 fold, heart failure risk by 3 fold and mortality risk by 1.5 to 1.9 times.\(^3-5\) Current strategies for predicting AF onset focus on identifying the familial,\(^6\) genetic,\(^7-9\) echocardiographic,\(^10\) and biological\(^11\) associations of increased AF risk.

The National Heart Lung and Blood Institute’s Workshop on AF emphasized identification of non-invasive biomarkers and assessment of their contribution towards AF risk.\(^12\) **P wave indices** constitute an electrocardiographic (ECG) biomarker associated with AF and may serve as an intermediate phenotype associated with AF risk. P wave indices include **PR duration, P wave duration, amplitude, area, and terminal force**.

P wave indices have been associated with incident AF and stroke in the ARIC Study.\(^13\) Similarly, in the National Health and Nutritional Examination Study (NHANES III), prolonged P wave duration has been associated with all-cause and cardiovascular mortality.\(^14\) Cross-sectional studies have demonstrated that subjects with risk factors for AF including hypertension,\(^15\) obesity,\(^16-18\) diabetes\(^19\) and sleep apnea\(^20\) have prolonged P wave indices compared to healthy controls. Investigation of P wave indices hypothesizes that P wave indices are a barometer of atrial electrophysiologic function. Subacute and chronic clinical insults such as obesity, hypertension and diabetes yield an inflammatory atrial substrate.\(^21-23\) The histopathologic end result is progressive atrial fibrosis and impaired intra- and interatrial electrophysiology,\(^24\) as manifested by the progressive alteration of P wave indices.

Significant questions persist in understanding the epidemiology of P wave indices and their modulation by clinical disease. The significant majority of prior P wave indices reports have been limited by small sample sizes with poor statistical power, selection biases, lack of adjustment for potential confounders, cross-sectional study designs, brief follow up, and deficits in measurement technique and reproducibility. No study has reported on longitudinal change in P wave indices. As a result, longitudinal evaluation of P wave indices and the association with clinical correlates remain unexplored.

P wave indices’ availability in ARIC is a unique opportunity for continued assessment of the epidemiology of P wave indices. This analysis will utilize a highly reproducible measurement with demonstrated integrity in a community-based, prospective cohort with comprehensive clinical characterization and long-term follow-up.

5. **Main Hypothesis/Study Questions:**
Primary hypothesis:
We hypothesize that each of the distinct P wave indices will demonstrate significant longitudinal prolongation and alteration in prospective analyses. We further hypothesize that obesity, hypertension and diabetes will be associated with greater prolongation and alteration of P wave indices.

Secondary hypothesis 1:
We hypothesize effect modification by race for alteration of P wave indices in longitudinal analysis.

Secondary hypothesis 2:
We hypothesis additional effect modification by race in the clinical correlates associated with greater prolongation of 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).

Design. The analysis is a prospective, longitudinal assessment of P wave indices across ARIC exams. The analysis will examine the change in P wave indices, described as prolongation and alteration. The primary hypothesis is that P wave indices will demonstrate longitudinal change across ARIC exams and, second, that such longitudinal change will be modified by specific clinical correlates (body mass index, hypertension, and diabetes).

Inclusion/exclusion.
We will exclude subjects with missing, inadequate or inaccurate P wave measurements in at least 2 of the 4 ARIC exams. Specific exclusion criteria by ECG include pre-excitation (Wolff-Parkinson-White), second degree Mobitz II, complete heart block, PR interval <80 or > 320, pacemakers, and presence of right or left bundle branch blocks. Clinical exclusion criteria at exam 1 include prevalent AF or AF on initial ECG and prevalent heart failure. We will also exclude the small number of individuals with a race/ethnicity other than white/African-American, and those missing covariates of interest in all 4 visits.

Subjects lacking covariates at their initial visit will likewise be excluded. Subjects lacking covariates at subsequent visits will have their prior visit’s values imputed.

Variables of interest and covariates.

<table>
<thead>
<tr>
<th>Clinical correlates</th>
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<tbody>
<tr>
<td>Age</td>
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<td>Sex</td>
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<tr>
<td>Race</td>
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<tr>
<td>Site</td>
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<tr>
<td>Education</td>
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<tr>
<td>Body mass index</td>
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<td>Waist circumference</td>
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</table>
Cigarette smoking
Alcohol intake, moderate or heavy (7 grams/week for women and 14 grams/week for men)
Diabetes
Ratio of Total to HDL cholesterol
Systolic blood pressure
Diastolic blood pressure
Use of antihypertensive medication
Prior myocardial infarction
Prior stroke
Prior heart failure
Medications (cardiac glycosides, beta-blockers, calcium channel blockers, antiarrhythmics class I and III)

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

Summary of data analysis. We will determine the distributions of P wave indices across exams, verifying their consistency with previously published analyses using these data in ARIC. We will then use multilevel modeling to describe the longitudinal progression of P wave indices and the clinical correlates for this progression in each ARIC subject. Such an approach has been utilized to examine echocardiographic traits in the Framingham Heart Study across exams.\textsuperscript{25} Multilevel modeling permits the inclusion of subjects missing interim data points by incorporating longitudinal data for each subject. We will examine the multilevel models in subjects missing data points and compare them to subjects who attended all 4 ARIC visits. Separate models for each P wave index will include a random intercept and fixed effects for the index and covariates as well as interaction terms between these variables and follow-up time. Covariates to be included are those previously associated with P wave indices in prior ARIC analyses (age, sex, race, BMI, waist circumference, systolic blood pressure, diastolic blood pressure) and those likely associated with P wave indices by pathophysiologic mechanisms (incident myocardial infarction, heart failure, ECG LVH). Other clinical, laboratory and social variables will be introduced in comprehensive modeling. Examination will be included as a model to account for differences in ECG technology platforms. Effect modification by race will be examined in all models. Statistical interactions will be assessed for relevant variables as informed by prior study of P wave indices. Subjects developing AF or heart failure will be censored.

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 #1611 P wave indices and obesity (Magnani) – cross-sectional analysis studying the association of obesity and metabolic syndrome with P wave indices. The new proposal focuses on changes of PWIs over time.

MS #1584 Long-term clinical outcomes of P wave indices (Magnani). It studies the association of P wave indices at baseline with CVD outcomes and mortality.

MS #1559 P wave indices and atrial fibrillation (Alonso). Focuses on the association of P wave indices at baseline with AF risk during follow-up.

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


