1. **Full Title:**
Is low Heart Rate variability (a marker of autonomic dysfunction) the missing link between Migraine with visual aura and Cardioembolic stroke?

2. **Abbreviated Title (Length 26 characters):**
Migraine with visual aura and low heart rate variability

2. **Writing Group:**
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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**: October 2018 (proposal submission)  
January 2019 (data acquisition)  
November 2019 (manuscript submission)

4. **Rationale**:  
Migraine with visual aura (MA) has been associated with an increased risk of stroke (1,2), specifically cardioembolic stroke (CES) (3). Among various pathophysiological mechanisms postulated for this association, autonomic dysfunction among the population with MA (4) may play a key role. However, this association has not previously been studied in any large cohort study to date.

Heart rate variability (HRV) is a reliable and commonly used clinical marker for autonomic nervous system dysfunction (5). Heart rate is regulated by a balance between the parasympathetic and sympathetic nervous systems. Autonomic dysfunction leads to differences in heart rate, which are measurable through HRV. Low HRV has been associated with cardiovascular disease risk factors and multiple cardiovascular outcomes, including atrial fibrillation (AF) (6) and increased risk of stroke (7).

In a recent study utilizing ARIC dataset we showed MA is a risk factor for incident AF (Sen et al. accepted for publication in Neurology green journal MS# 2977). The important question that remains unanswered is if the association between MA and CES may be explained by a higher rate of autonomic dysfunction in this subgroup.

Therefore, we propose to study the association between migraine with aura and reduced HRV as a potential mechanism explaining the previously reported association between migraine with aura, AF and CES. The following is a schematic diagram of the proposed hypothesis:
5. **Main Hypothesis/Study Questions:**

   i) Is MA (in contrast to migraine without aura) independently associated with low HRV, a marker of cardiac autonomic dysfunction?
   
   ii) To determine if the relationship between MA and CES is mediated by autonomic dysfunction (low HRV) within this cohort.

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:**
   
   **Inclusion/Exclusion:**

   Participants in the ARIC study completed a third clinic examination (1993 to 1995), when a lifetime history of headaches was ascertained. During a subsequent follow-up visit (Visit 4; 1996-1998) HRV was measured using 6-minute EKG. Participants who completed both visits will be included within the analysis. Participants with missing headache information and those who have missing information for HRV will be excluded. Subjects with history of atrial fibrillation (prior to visit 3) will also be excluded. Those with race other than whites or black will be excluded due to limited sample size.

   **Main exposures of interest:**

   Headaches will be classified at earlier visits as migraine with visual aura, migraine without aura, or non-migraine headaches (8).

   **Main Outcome:**

   Our primary outcome is HRV. ARIC measured HRV twice: (1) 2-minute ECG readings at visit 1 and (2) 6-minute ECG readings at visit 4. For the purpose of our study we will use the HRV measures from visit 4 only. HRV indices are commonly divided into time and frequency domain measurements. In ARIC, HRV indices for time and frequency domains were calculated using the standard deviation of RR intervals (SDNN), the mean of all normal RR intervals (MeanNN), the root mean square of successive differences of successive RR intervals (RMSSD), low (LF) and high (HF) frequency power, and the LF/HF ratio. All HRV measures will be categorized into quintiles.

   For our secondary analysis, In order to test the link between MA-HRV-CES, we will also look to see if the relationship between HRV and CES is mediated by autonomic dysfunction (low HRV) among this population.

   **Co-variates:** Age, gender, education, race (categorized as white, black, or other), smoking status, alcohol use, coronary artery disease (CAD)) assessed by self-report. Body mass index
(BMI) calculated as weight in kilograms divided by height in meters squared. Hypertension defined as a systolic blood pressures of 140 mmHg or higher, a diastolic blood pressure higher than 90 mmHg, or use of medications to treat hypertension. Diabetes as determined by self-report of a physician diagnosis of diabetes, non-fasting blood glucose level of 200 mg/dL or higher, fasting blood glucose level of 126mg/dL or higher, or use of insulin or other oral hypoglycemic medications. Physical activity is considered significant if performed for 4 hrs/week for at least a month. Prevalent CAD was defined by electrocardiographic evidence of previous myocardial infarction (MI), history of physician diagnosed MI, or previous coronary revascularization procedure (bypass, angioplasty). Medications including use of beta blockers, antimigraine drugs and oral contraceptives, and antiplatelet drugs.

**Statistical analysis:**
All participants, with or without migraine, will be assessed for follow-up data on HRV indices. All HRV measures will be categorized into quintiles. Multinomial logistic regression models will be used to estimate ORs for the relationship between MA and HRV measures. Several models may be run including covariates --demographic (i.e. age, race, sex) and vascular risk factors (i.e. BMI, physical activity, hypertension, smoking, alcohol, socioeconomic status, CAD and medications (example beta blockers, antimigraine drugs and oral contraceptives)). These covariates will initially be assessed for evidence of significant confounding of MA and HRV, before being included in a final model.

We would be also examining if HRV is a potential mediator between the relation between MA and CES. Mediation analysis will be conducted using Barron-Kenny’s causal step tests (9).

<table>
<thead>
<tr>
<th>Exposure Variable</th>
<th>Migraine with visual aura</th>
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<tbody>
<tr>
<td><strong>Outcome Variable</strong></td>
<td>HRV indices for time and frequency domains (RR intervals (SD\textsubscript{NN}), the mean of all normal RR intervals (Mean\textsubscript{NN}), the root mean square of successive differences of successive RR intervals (RMSSD), low (LF) and high (HF) frequency power, and the LF/HF (ratio)</td>
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<td>All HRV measures will be categorized into quintiles.</td>
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<tr>
<td><strong>Secondary Outcome</strong></td>
<td>Cardioembolic Stroke (to test if HRV as an mediator of the relation between MA and CES)</td>
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<td><strong>Covariates</strong></td>
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<td>Diabetes</td>
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Limitation:

1. Headache classification: Headache classification criteria used in previous ARIC publications is different from the ICHD III criteria published in 2018. The migraine criteria used in ARIC is much stricter and more likely to have missed migraine diagnoses in patients who presented with bilateral headache, or lasted less than one year, or had history of migraine at younger ages, but likely have included migraineurs with high frequency migraine episodes in mid to later life.

2. Finally, one limitation may be lack of details and ascertainment of migraine medications (example Propranolol and triptans) that influence heart rate, specifically during visit 3 and 4.

Despite the limitations, this is the first cohort study to evaluate association between migraine and chronic autonomic dysfunction as measured through HRV. This finding will have important clinical implications and may help us better understand the migraine-stroke link. A randomized clinical trial may help ascertain if migraine with visual aura with chronic autonomic dysfunction may benefit from monitoring for AF detection and subsequent anticoagulation or antiplatelet therapy as a primary stroke prevention strategy.

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

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.

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Analysis</th>
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<td>Alcohol use</td>
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<td>CAD</td>
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<td>Medications</td>
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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)?

None to report

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

11.b. If yes, is the proposal
___ A. primarily the result of an ancillary study
___ 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:


