ARIC Manuscript Proposal #3850

PC Reviewed: 5/19/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The association between heart rate variability and agitation in Alzheimer's disease: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters):
HRV and agitation in AD

2. Writing Group:
Writing group members:
Dr Kathy Liu
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __KL___ **[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:
Aim to obtain, analyze and write up study for publication by August 2022.

4. Rationale:
Heart rate variability (HRV), the beat-to-beat variation in heart rate, has long been considered a marker of cardiovascular risk[1,2], but is increasingly studied in relation to neural and cognitive processes. HRV is under predominant parasympathetic control[3,4] and influenced by a network of brain regions involved in autonomic nervous system regulation, known as the central autonomic network[5]. This network, which comprises prefrontal cortical (anterior cingulate, insula, orbitofrontal, and ventromedial cortices), limbic (central nucleus of the amygdala, hypothalamus), and brainstem regions, significantly overlaps with regions involved in 'top-down', self-regulatory neural processes such as emotion regulation and executive functioning. This has led to the proposal that vagally-mediated HRV may index these aspects of prefrontal cortical function[6–8].

Impairments in executive dysfunction and emotion regulation have been hypothesized to underlie common and difficult-to-treat neuropsychiatric symptoms in dementia, including agitation, disinhibition and apathy[9,10]. Agitation, defined as sustained, observed or inferred evidence of emotional distress associated with excessive motor activity, verbal aggression or physical aggression[11], is a common, distressing and difficult-to-treat neuropsychiatric syndrome in dementia. A major barrier to the identification of better, safer and more targeted drug therapies has been the lack of understanding of the neurobiology of agitation and identification of valid biomarkers [12,13]. It is important to investigate the potential of HRV as a valid and easy-to-obtain physiological marker of emotion regulation capacity, which could be used to evaluate and monitor patients with dementia who have difficulty reliably self-reporting their emotional states.

In healthy adults, higher HRV is linked to better cognitive function[14], including in older individuals[15–17], and is associated with better top-down self-regulation processes (including executive functioning, emotion regulation, and effortful or self-control)[18]. Neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD), can reduce the integrity of the central autonomic network and are associated with cardiovascular sympathovagal imbalance, abnormal emotional reactivity[19–22] and lowered HRV[23,24]. We also found in a systematic review and meta-analysis that HRV measures at rest and in response to a task were related to better cognitive and behavioral performance in neurodegenerative disorders (Liu K, et al. *under review*). Specifically, these HRV indices were high-frequency (HF-HRV) and root mean square of successive R-R interval differences (RMSSD), which have been described to be vagally-mediated and are interpreted to be more specific to parasympathetic function [1,25]. However, most included studies were cross-sectional and no previous study has investigated the longitudinal relationship between HRV and agitation.

The Atherosclerosis Risk in Communities study provides a unique opportunity to examine the potential link between HRV and incident agitation in neurodegenerative conditions such as Alzheimer's disease.

See end of document for references.

5. Main Hypothesis/Study Questions:
The study primarily aims to investigate whether lower heart rate variability (HRV) is associated with incident agitation in Alzheimer's disease (AD). Specifically, the study will ask:

a. Is there a cross-sectional relationship (i.e. between HRV and agitation at Visit 5)?
b. Is there a longitudinal relationship (i.e. between HRV at Visits 1-5 and agitation incidence at Visits 5-7)?

A secondary analysis is to explore possible neural mechanisms using structural MRI data of specific brain regions (Visit 5) involved in emotion regulation.

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:
This study will use ARIC data to assess the cross-sectional and longitudinal relationship between HRV and agitation in AD, and explore whether this could be influenced by emotion regulation capacity.

ARIC participant inclusion criteria:
1) Has AD
   - Any participant who has been indicated as having AD or AD dementia or mild cognitive impairment (early-stage AD) on any ARIC questionnaire.
   - If there are insufficient participants with AD, we will expand our analysis to include additional dementia types or neurodegenerative conditions, e.g. PD.
2) Had heart rate variability indices (RMSSD and/or HF-HRV) measured on at least one occasion (see below for timepoints)
3) Completed the Neuropsychiatric Inventory (NPI) on at least one occasion (see below for timepoints).

Measures of interest:
- Heart rate variability indices
  - This will include resting RMSSD +/- HF-HRV, which have been proposed to be more specific to parasympathetic function.
  - HRV was measured at
    a) Visits 1-5 based on 10sec resting ECG (RMSSD only)
    b) Visit 1 based on 2 min resting ECG (RMSSD and HF-HRV)
    c) Visit 4 based on 6 min resting ECG (RMSSD and HF-HRV)

- Agitation measures
  - This will primarily be the presence or absence of agitation symptoms on the NPI scale.

- The severity of agitation is also measured on this scale and its relationship to HRV will be explored.
- Presence of agitation will be defined as a positive Agitation/aggression subscore (narrow definition), and a composite score (≥3) of NPI-rated Agitation/aggression, Disinhibition, Motor overactivity and Irritability/Lability (broad definition).
- NPI score was measured at Visits 5, 6 and 7.

Data analysis:

-Cross-sectional assessment

- Examine whether differences in HRV(RMSSD) are related to presence/absence of agitation in AD at Visit 5 using log regression.
- Include age, sex, cognitive status (e.g. MMSE score), years of education, study site ('center') and vascular risk factor status (e.g. QRisk score indicating history of myocardial infarction, diabetes mellitus, smoking status, beta-blocker medication) to see if the relationship differs in the presence of these characteristics.
- Explore the relationship between agitation severity and HRV measures using the Pearson correlation coefficient.

-Longitudinal assessment

- Examine whether differences in mean HRV (RMSSD or HF-HRV across Visits 1-5) predicts (any) incident agitation during Visits 5-7 using log regression.
- Examine whether longitudinal change in HRV (Visits 1-5) is associated with incident agitation during Visits 5-7 in Alzheimer's disease participants, using a latent growth curve model.
- Include age, sex, cognitive status (e.g. MMSE score), years of education, study site ('center') and vascular risk factor status (e.g. QRisk score indicating history of myocardial infarction, diabetes mellitus, smoking status, beta-blocker medication) in the above models to see if the relationship differs in the presence of these characteristics.

-Neuroimaging / emotion regulation measures

- We will explore whether MRI brain region volume measures (obtained at Visit 5), proposed to be related to emotion regulation, influence or mediate any relationship between HRV and agitation using a structural equation model. MRI volumes of interest will include amygdala, medial prefrontal cortex, lateral orbitofrontal cortex, basal forebrain, and insula. We will also explore the feasibility of combining the ARIC dataset with other AD datasets (that also include agitation/MRI/emotion regulation measures) to assess model fit.

Anticipated challenges:

The power to detect an effect will depend on the sample size of eligible participants and degree of missing data. Over 2500 participants completed the NPI at Visit 5, and the prevalence of agitation increases with disease progression. If the sample size for AD participants is insufficient for the analyses, I will widen eligibility criteria to include other neurodegenerative conditions e.g. PD and those with "dementia". The feasibility of combining ARIC data with other datasets

in a structural equation model will also depend on the degree of missing data/pairwise correlations between the datasets.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes _x___ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 current derived consent file ICTDER05 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/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)?
We have already contacted Prof Heiss, who published work on HRV using the ARIC dataset, and he has provided helpful comments and introduced Dr Whitsel. Both will collaborate with us for the proposed study.

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 (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 https://sites.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.

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