ARIC Manuscript Proposal #3894

PC Reviewed: 7/13/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The role of left atrial function in mediating the association between blood pressure and neurocognitive outcomes

b. Abbreviated Title (Length 26 characters): BP, LA, stroke/dementia

2. Writing Group:
Writing group members: Jeremy R. Van't Hof, Romil Parikh, Anne Eaton, Riccardo M. Inciardi, Pamela L. Lutsey, Alvaro Alonso, Kunihiro Matsushita, Rebecca Gottesman, Michelle Johansen, Scott D. Solomon, Amil M. Shah, Lin Y. Chen, others welcome

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

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3. Timeline: Statistical analysis: 3 months
Manuscript preparation: 6 months

4. Rationale:

1. Atrial myopathy is associated with stroke and dementia.

Accumulating evidence indicates that atrial myopathy—characterized by abnormalities in left atrial (LA) size or function—are associated with increased risk of stroke and dementia, independent of atrial fibrillation (AF).[1–5] In MESA participants, those with the lowest tertile of LA ejection fraction had a 50% increased risk of incident ischemic cerebrovascular events compared with the highest tertile after adjusting for cardiovascular risk factors and atrial fibrillation.[2] Both lower LA reservoir and conduit strain were associated with higher risk for stroke in a hospital-based cohort of patients with AF.[3] In another hospital based sample of patients without AF, each 1% drop in LA reservoir strain was associated with a 7% increased risk in cryptogenic stroke or transient ischemic attack.[4] The association of atrial myopathy with dementia or cognitive impairment is theorized, but the epidemiological data are limited.[6–8]

2. Hypertension increases risk for stroke and dementia.

Hypertension is a well-established risk factor for stroke, increasing the likelihood of stroke 3-fold compared with individuals with normal blood pressure.[9] Early to midlife hypertension is particularly important in terms of risk for stroke later in life.[10,11] There is also growing evidence for increased incidence of dementia and cognitive impairment in those with midlife hypertension. In ARIC, higher midlife systolic blood pressure (SBP) was associated with a steeper cognitive decline, although this finding was only present in white adults.[12] ARIC participants with midlife hypertension and both hypertension and hypotension in late life had a 50-60% increased risk for incident dementia.[13] In a younger sample of patients in the Kaiser Permanente health system, midlife hypertension was associated with a 65% increased risk for incident dementia for women, but no increased risk for men; early adulthood hypertension was not associated with dementia.[14] However, in a younger cohort of CARDIA participants, Suvila et al. showed that early onset hypertension was associated with cognitive decline in middle adulthood.[15]

3. Cumulative blood pressure can lead to left atrium abnormalities.

Multiple studies have evaluated the relationship between hypertension and LA abnormalities. A recent study from ARIC by Teramoto et al. evaluated the association between time-averaged cumulative blood pressure and echo findings as well as incident heart failure.[16] The only left atrial parameter that was evaluated was LA volume index, which increased with higher blood pressure. Cumulative SBP was associated with increased risk for incident heart failure and >50% of the association was accounted for by echocardiographic changes. Cumulative blood pressure affects more than just LA volume. Using data from the CARDIA study, Vasconcellos et al. reported an association between cumulative SBP over 30 years and i) increased left atrial volumes; ii) increased active emptying volume; and iii) abnormal early diastolic left atrial strain.[17] Changes in

LA strain can predate change in volume in patients with both hypertension and diabetes.[18]

Based on the prior research above, we hypothesize that the well-established association of elevated SBP with stroke and dementia is partially mediated by abnormalities in LA size or function.

5. Main Hypothesis/Study Questions:

1. Quantify the extent to which LA size and function mediate the association between blood pressure and (1) stroke; (2) dementia.

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

Prospective association of BP exposures (Visit 1 – 5) with stroke and dementia after Visit 5. The mediators (LA size and function) will be assessed at Visit 5.

Study population

Inclusion criteria: ARIC participants with 2D echocardiographic LA size and function data at Visit 5

Exclusion criteria: Participants diagnosed with stroke (for Outcome 1) or dementia (for Outcome 2) at or prior to Visit 5; participants diagnosed with atrial fibrillation at or prior to Visit 5; missing or low quality echo data at Visit 5; race other than white or black; non-whites in the Minneapolis and Washington County field centers; those missing covariates.

Exposure/independent variables:

We will evaluate blood pressure using values from Visits 1-5. The primary exposure will be cumulative SBP defined in the following ways:

1. Time-averaged cumulative SBP: the sum of averaged SBPs from adjacent consecutive visits, indexed to the total exposure time from V1 to V5.[16]
2. Time-averaged cumulative underlying SBP: using the method employed by Teramoto et al to account for antihypertensive medication use.[16,19]

Mediating variables: all measured at visit 5

Primary

1. LA reservoir strain

2. LA emptying fraction

Secondary

1. LA passive emptying fraction
2. LA active emptying fraction
3. LA conduit strain
4. LA contractile strain
5. LA maximum volume index
6. LA minimum volume index

Outcomes

1. Incident ischemic stroke after visit 5
2. Incident dementia after visit 5—adjudicated cases from visit 6, annual surveillance of hospital and death records, telephone interviews[13,20]

Covariates

The following variables, measured at Visit 5, will be considered for inclusion in our models: age, sex, race, current cigarette smoking, lipid lowering medications, anticoagulants, and anti-platelet agents, HDL, LDL, triglycerides, diabetes, ApoE**,** eGFR, prevalent heart failure, prevalent coronary heart disease, left ventricular global longitudinal strain, E/E'.
We will include BMI, alcohol use and physical activity as time varying covariates measured in Visits 1-5.

Statistical analysis

- Baseline characteristics of participants will be described using means and proportions stratified by level of exposure to hypertension
- Incidence of stroke and dementia will be calculated and stratified by level of exposure to hypertension
- Cox proportional hazards regression will be used to evaluate the relationship between SBP exposure and incident stroke and dementia.

- Model 1 will adjust for age, sex, and race/center
- Model 2 will additionally adjust for current cigarette smoking, alcohol use, BMI, physical activity, statins, anticoagulants, and anti-platelet agents, HDL, LDL, triglycerides, diabetes, ApoE**,** eGFR, left ventricular global longitudinal strain, E/E'
- Model 3 will additionally adjust for prevalent heart failure, prevalent coronary heart disease

- We will conduct mediation analyses to examine the controlled direct effect, the natural direct effect, and the natural indirect effect of BP exposures on outcomes with mediation by LA size and function using an approach developed by Valeri and Vanderwheel.[21,22] This will involve one fully adjusted model using the covariates in Model 3 above.
- We will perform sensitivity analyses excluding participants with prevalent heart failure, chronic kidney disease and coronary heart disease at Visit 5.

- Interactions by race and sex will evaluated using cross-product terms.

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 __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.
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)?
The most relevant manuscript proposals include:
- MS 3750: Association of Left Atrial Function with Neurocognitive Outcomes in the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS)
- MP# 3051. The association of middle and late-life blood pressure with conversion to MCI and dementia: The ARIC Study

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

2015.29

11.b. If yes, is the proposal
_x__ A. primarily the result of an ancillary study (2015.29)

___ **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.

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