1.a. **Full Title**: Prevalence and characteristics of intracranial arterial dolichoectasia in the ARIC study

   b. **Abbreviated Title (Length 26 characters)**: IADE in ARIC

2. **Writing Group**: Melissa Caughey, Li Liu, Kevin Sam, Ningdong Kang, Wenjie Yang, Zhongqing Huang, Jose Gutierrez, Gerardo Heiss, Bruce Wasserman, Ye Qiao

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. 

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3. **Timeline**: Manuscript to be completed within 1 year
4. **Rationale:**

The broad objective of this project is to conduct a descriptive, cross-sectional epidemiologic investigation of intracranial arterial dilation and tortuosity (dolichoectasia) in the elderly general population. Intracranial arterial dolichoectasia (IADE) is an age-related arteriopathy, defined by an increase in tortuosity and diameter of at least one intracranial artery. Although frequently silent, IADE has been associated with stroke and cognitive decline. The arterial geometric distortion likely contributes to atherosclerosis, thrombus formation, hypoperfusion, and intracerebral hemorrhage. Normal blood flow is disrupted by IADE, creating regions of chronic and uneven wall shear stress. High shear stress exacerbates vascular tortuosity, while regions of low shear stress are known to promote atherosclerotic plaque formation. Kinks and sharp angles divert the blood flow through tortuous segments, impeding the normal passage to branching vessels and possibly causing hypoperfusion and leukoaraiosis. Additionally, dilated arterial segments create slow blood flow and bidirectional eddies; conditions favorable for blood clot formation leading to infarction. IADE is also characterized by thin, weakened arterial walls which may balloon outwards and rupture, possibly causing cerebral microbleeds or hemorrhagic stroke.

Despite its important consequences, IADE has received little attention compared to other vascular diseases such as intracranial atherosclerosis. Our current understanding of IADE has largely been drawn from patients with a clinical need for brain imaging, such as hospital-based cohorts and patients suffering a stroke. Examinations of IADE in asymptomatic populations have been scarce and classified solely by arterial dilation. However, a recent investigation from the Northern Manhattan Stroke Study examined basilar artery elongation, a surrogate for tortuosity, and its association with all-cause mortality. While IADE is characterized by dilatation and tortuosity, these 2 phenotypes are likely to have differing determinants and clinical outcomes. We propose to stratify IADE into 3 groups (isolated tortuosity, isolated dilation, and combined tortuosity + dilation), and describe its prevalence and clinical associations in the elderly general population. To accomplish this, we will analyze MRI and clinical data from ARIC visit 5.

5. **Main Hypothesis/Study Questions:**

1. What is the prevalence and phenotypic distribution (isolated tortuosity, isolated dilation, combined tortuosity + dilation) of IADE in the elderly general population?
2. What is the artery-specific (basilar artery, anterior cerebral artery, middle cerebral artery) prevalence and phenotypic distribution of IADE?
3. What are the cross-sectional demographic and clinical characteristics of ARIC participants with vs. without IADE?
4. Is small vessel disease (subclinical infarctions, leukoaraiosis, microbleeds) more often observed in the vascular territories of dolichoectatic arteries?
5. Do participants with IADE more often have history of stroke or evidence of stroke on MRI, and does this association differ by IADE phenotype or specific artery? Is evidence of stroke more often in the vascular territories of dolichoectatic arteries?
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 Population: ARIC participants with an interpretable brain MRI scan from visit 5

Arterial Dilatation: Arterial diameters, cross-sectional area, and volumes were quantified at visit 5 from magnetic resonance angiography using centerline segmentation from 3D images. Measurements were obtained at designated vessel segments (supraclinoid internal carotid artery (ICA), M1 segment of the middle cerebral artery (MCA), A1 segment of the anterior cerebral artery (ACA), and basilar artery (BA) over a fixed length for all participants. For the purposes of this analysis, arterial diameters will be indexed to the total estimated intracranial volume, which has previously been measured (variable =ETIV51).

Tortuosity: As outlined in R21 HL145509 (pending), we will examine tortuosity in the large intracranial arteries, which typically present with C-shaped curves when dolichoectatic, and are well quantified by the arc-chord ratio. This measure simply examines how long the curve is, divided by the straight distance between its two end points. As a sensitivity analysis, we will also analyze tortuosity in the visualized lenticulostriate arteries (LSA). The LSAs have previously been imaged from vascular wall MRI using 3D turbo spin-echo sequences with variable flip angles at ARIC visit 5.

IADE Classification: There is no standard, agreed-upon definition of IADE. Consistent with previous research, we will consider any extreme dilation or tortuosity (> 2 x standard deviation) in the BA, MCA, or ACA to be IADE. Dilation and tortuosity extremes will be assessed separately for women and men and for black and white participants. If substantial differences exist, classifications of IADE will be stratified by demographic subgroup. In a sensitivity analysis, we will also define IADE volumetrically, by >2 x standard deviation of the arterial volume. Previous investigations have indexed arterial volumes to the visualized arterial length, due to challenges imaging the entire length of the artery.

Analytic Plan: The primary analysis will be descriptive (t-tests, \( \chi^2 \) tests).

Limitations: The study population will be limited to participants undergoing brain MRI at visit 5. Those with insufficient image quality will need to be excluded.

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  ____x____ 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   ____ 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/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)?

This manuscript proposal is based on variables to be acquired through our ancillary study proposal (2015.33, “Prevalence, predictors, and outcomes of basilar artery dolichoectasia in the ARIC study”). Our R21 grant (HL145509) received a score within the zone of consideration and is likely to be funded.

A separate ancillary study proposal (2018.14, “Genetics of the circle of Willis and their role in stroke and Alzheimer’s disease risk”) was submitted by collaborators of this manuscript proposal (Wasserman, Gutierrez), with the aim of investigating cerebral hemodynamics and genetic locus related to dilatation as effect modifiers on the relationship between brain arterial dilatation and cognitive decline.

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

11.b. If yes, is the proposal

 ____ x ____ A. primarily the result of an ancillary study (list number* _2015.33____)

 ____ 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 https://www2.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

References


