

ARIC Manuscript Proposal #3486

PC Reviewed: 10/8/19
SC Reviewed: _____

Status: _____
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Priority: 2
Priority: _____

1.a. Full Title: Carotid-femoral pulse wave velocity and cerebral large artery remodeling. The ARIC Study.

b. Abbreviated Title (Length 26 characters): PWV - cerebral arterial diameter

2. Writing Group members: (Alphabetic) Melissa Caughey, Kamakshi Lakshminarayan, Kunihiro Matsushita, Michelle Meyer, Priya Palta, Ye Qiao, Hirofumi Tanaka, Bruce Wasserman

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

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3. Timeline: Anticipated completion of a manuscript within 8 mos.

4. Rationale:

It has been reported that the cerebral large arteries experience age-related outward remodeling characterized by degenerative changes such as loss of elastin and gaps in the internal elastic lamina (IEL), concentric thickening of the wall, and dilation with maintenance of the lumen-to-wall ratio.¹

Although an increase in elastin fibers follows high shear stress it was posited that hemodynamic factors are the most likely explanation for age-related arterial changes,² and outward remodeling is

reportedly mediated by metalloproteinase cleavage of elastin, increasing the vulnerability of the arterial to dilation.^{3,4} The hypothesis that the mechanical forces of blood flow are the a driver of arterial aging is supported by animal models⁵ and pathology studies.¹ Age-related remodeling primarily affects the more proximal arteries such as the intracranial internal carotid artery, the basilar artery, and the circle of Willis.⁴

Dilated brain arteries likely represent low impedance to flow. In turn, increased central arterial stiffness increase the susceptibility of the cerebral small vessels to pulse-wave velocity and pulsatility, probably mediated by dilated brain large arteries.^{6,7} The hypothesis that the mechanical forces of blood flow are the a driver of arterial aging is supported by animal models⁵ and pathology studies.¹

Brain arterial dilation has been related to a higher risk of Alzheimer's Disease (AD).⁸ Among individuals of a mean age of 77 yrs. followed for an average of 3 yrs., larger intracranial carotid diameters increased the risk of AD, after adjustment for vascular risk factors, APOEε4 and white matter hyperintensities.⁸ Cross-sectional analyses of the ARIC cohort Visit 5 examinees on the other hand identified associations between central artery stiffness and pulsatility and structural brain damage, poorer cognitive performance, mild cognitive impairment, and dementia.^{9,10} We propose to examine the hypothesized association of central artery stiffness and pulsatility with cerebral large artery diameters.

5. Main Hypothesis/Study Questions:

- i. We hypothesize that carotid-femoral pulse wave velocity (cfPWV) and central pulse pressure are (directly) associated with cerebral large artery diameters.
- ii. We posit that cfPWV and central pulse pressure are associated with cerebral artery length and (also) tortuosity.

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).

Measurements

PWV was measured using the automated waveform analyzer VP-1000 Plus (Omron Co., Ltd., Kyoto, Japan) after participants were supine for 5 to 10 minutes. Carotid and femoral arterial pressure waveforms were acquired by applanation tonometry sensors on the left common carotid artery and left common femoral artery. Bilateral brachial and posterior-tibial arterial pressure waveforms were detected by plethysmographic and an oscillometric pressure sensor wrapped on both arms and ankles. PWV was calculated as distance divided by transit time. Distance for carotid femoral PWV (cfPWV) was measured with a segmometer (Rosscraft, Surray, Canada) and calculated as the carotid to femoral distance minus the distance between the suprasternal notch to carotid. Technicians obtained two measurements and the results were averaged.

Axial arterial diameters, cross-sectional area, and volumes were quantified at ARIC Visit 5 from magnetic resonance angiography using centerline segmentation from 3D images. Measurements were obtained at pre-specified 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 (variable =ETIV51).

The presence of tortuosity was quantified by the arc-chord ratio, relating the length of the curve to the linear distance between the end points of the segment measured.

Analytic approach

The analyses will be cross-sectional; descriptive statistics will be used to relate carotid-femoral pulse wave velocity and central pulse pressure (interval scale) to arterial diameters (indexed to total estimated intracranial volume) at the ICA, MCA, ACA and BA images. Descriptive statistics will be used to relate carotid-femoral pulse wave velocity and central pulse pressure (interval scale) to arterial length and the presence of tortuosity at the ICA, MCA, ACA and BA images, as indexed by the arc-chord ratio.

References

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7.a. Will the data be used for non-CVD analysis in this manuscript? Yes 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 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.csc.unc.edu/aric/mantrack/maintain/search/dtSearch.html>

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 found

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

11.b. If yes, is the proposal

A. primarily the result of an ancillary study (list number* 2015.23 and 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.csc.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.csc.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.