ARIC Manuscript Proposal # 2920

PC Reviewed: 1/10/2017 Status: _____ Priority: 2
SC Reviewed: _____ Status: _____ Priority: ____

1a. **Full Title**: Arterial Stiffness and Pulsatility and Intracranial Atherosclerosis: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Arterial stiffness and Intracranial Atherosclerosis

2. **Writing group**: (Alphabetical): Mike Griswold (invited), Gerardo Heiss, Timothy Hughes, David Knopman, Ye Qiao, Priya Palta, Bruce Wasserman, Jingkai Wei

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

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3. **Timeline**: Analyses to start upon approval of proposal. Submit for publication within 9 months from proposal approval.

4. **Rationale**:

Vascular aging is associated with stiffening of the aorta and arterial segment-specific loss of arterial elasticity, largely due to arterial remodeling with replacement of elastin with collagen,[1] resulting in higher pulsatility.[2] Organs with high flow and low microvascular impedance such as the brain and kidneys are particularly sensitive to excessive pressure and flow pulsatility.[3] The increased penetration of excessive pulsatile energy into the microvascular bed induced by aortic stiffening is associated with microcirculatory remodeling, impaired reactivity, and repeated episodes of microvascular ischemia and tissue damage.[4] Microvascular ischemia in the brain is associated with white matter hyperintensities and small, subclinical focal brain infarcts, and ultimately with cognitive impairment and dementia (**Figure 1**).[3,5-8]

Increased central pulsatility is also reported to increase the risk of extracranial atherosclerosis.[9] Intracranial atherosclerotic disease (ICAD), characterized by the presence of plaques – with or without stenosis – of the larger cerebral arteries – has not been widely studied in relation to arterial stiffness or pulsatility. A hospital-based retrospective study tested the association between pulse wave velocity (PWV) and cerebral atherosclerosis in a sample of stroke patients, and additionally compared differences in the associations observed for extracranial versus intracranial arteries.[10] Using a peripheral measure of PWV, investigators observed a higher PWV to be associated with the presence of intracranial atherosclerosis, defined as ≥50% stenosis, and a combined metric of intra- and extra-cranial atherosclerosis, but not with extracranial atherosclerosis alone.[10]

The literature documents a strong association between arterial stiffness and risk for ischemic stroke,[11] as part of increasing indications that end-organ damage due to increased central arterial stiffness is observed in the brain. Specifically ICAD is the most common cause of ischemic stroke[12] and pulse wave velocity among those with a history of stroke has been observed to be higher compared to those without stroke.

We propose to the test the hypothesis that central arterial stiffness and pulsatility, as measured by carotid-femoral pulse wave velocity (cfPWV) and estimated central pulse pressure (cPP), are associated with presence of ICAD, degree of intracranial plaque stenosis, and intracranial atherosclerotic burden. ARIC and its ancillary studies provides an opportunity to address this novel question at Visit 5 by drawing on high-resolution vascular sequences of 3D time-of-flight MRA and 3D high isotropic resolution black blood MRI (BBMRI), and segment-specific pulse wave velocity and estimated central pulse pressure.

5. Research Question(s):

Aim 1: Test the hypothesis that arterial stiffness and pulsatility measured in older adulthood are (directly) associated with increased odds of (a) ICAD, (b) intracranial stenosis (≥50%) and (c) intracranial atherosclerotic burden (i.e. number of plaques)

Aim 1.1: Characterize the distributions of cfPWV and cPP by number of intracranial plaques

Aim 1.2: Characterize the distributions of cfPWV and cPP by degree of plaque stenosis (no detectable stenosis, <50% stenosis, 51%-70% stenosis, 71%-99% stenosis, and occlusion)

6. Design and analysis

Study Population

Pulse wave velocity and central pressure pulsatility (PWV) were measured on 6,538 participants who attended ARIC-NCS Visit 5 (2011 - 2013), following a standardized protocol.[13] A subset of 1,980 examinees was selected for brain MR imaging by oversampling participants with evidence of cognitive impairment and having had a prior brain MRI. Those exams with adequate or excellent image quality and MRI protocol adherence (~1,755 examinees) will be included in these analyses.

Arterial Stiffness and Pulsatile Hemodynamics

PWV was calculated with the VP-1000 Plus; Omron Co., Kyoto, Japan, as the path length between arterial sites divided by the time delay between the foot of the respective pulse waveform. Carotid-femoral PWV (cfPWV) will be used as standard measure of arterial stiffness. Distance for cfPWV was measured over the surface of the body with a segmometer and calculated as (carotid to femoral artery distance) – (suprasternal notch to the carotid artery distance). Measurements were performed

twice for data quality purposes. Blood pressure was calculated simultaneously by the VP-1000 Plus to obtain estimated central carotid pulse pressure (cPP).

Throughout the study, a stratified sample of records was reviewed for quality by H. Tanaka (n=40 records per month), with quality grading and feed-back to the technicians at each field site. Based on 480 QC records evaluated per year, 78% of records were considered of optimal quality, 17% were of good quality, 3% were acceptable, and none were graded as poor or unacceptable quality. The intraclass correlation coefficients and 95% confidence intervals (95% CI) were 0.70 (0.59, 0.81) for cfPWV, and 0.60 (0.48, 0.72) for cPP.[14]

Intracranial Atherosclerosis

The MRI protocol has been described.[15][16] MRI scans were performed on 3.0T Siemens scanners and high-resolution vascular sequences were acquired at the end of a standardized brain MRI protocol and included 3D time-of-flight MRA and 3D high isotropic resolution black blood MRI (BBMRI) with acquired resolutions of 0.50×0.50×0.55 mm^3 and 0.50×0.50×0.50 mm^3, respectively. MRI images were analyzed by seven certified readers at the MRI Reading Center without knowledge of participant characteristics.

Atherosclerotic plaques were defined as wall thickening on reconstructed BBMRI images with or without luminal stenosis on MRA.[16] Plaques were recorded for vascular territories categorized as right and left internal carotid artery (ICA), right and left middle cerebral artery (MCA), right and left posterior cerebral artery (PCA), right and left anterior cerebral artery (ACA), basilar artery (BA), and right and left vertebral artery (VA). The degree of stenosis was recorded as <50%, 51%-70%, 71-99%, no detectable stenosis, and occlusion, and wall thickness, area, volume, and normalized wall index (NWI, wall area/outer wall area) were measured for the most stenotic plaque identified in each territory. Reliability estimates for plaque detection ranged from fair to good as reported by Qiao et al, 2016.[16]

Variables of interest

Exposure(s): Central arterial stiffness and pulsatility measures

1. Central carotid pulse pressure (cPP): [central systolic blood pressure – right brachial diastolic blood pressure]
2. Carotid-femoral pulse wave velocity (cfPWV)

- Note: Higher values of cfPWV and cPP indicate higher arterial stiffness and pulsatility

Outcome(s): Intracranial atherosclerotic disease (intracranial plaque presence), presence of intracranial stenosis (>50%), and intracranial atherosclerotic burden (i.e. number of plaques) measures

1. Qualitative variables:
- Presence of plaque (plaque)
- Total number of plaques (n_plaq)
- Presence of plaque by vessel segment (e.g., n_rmca_plaq, n_lmca_plaq, n_raca_plaq, etc)
- Degree of stenosis (zero to minimal luminal indentation, <50%, 50 to 70%, >70% and occlusion) (rmca_plaq_stenosis, lmca_plaq_stenosis, raca_plaq_stenosis, etc…)

2. Quantitative variables:
- MRA Area Degree of Stenosis (%)
- MRA Area Obstruction (mm2)
- MRA Diameter Degree of Stenosis (%)
- MRA Diameter Obstruction (mm)
- VWI Vessel Wall Area Segment Average (mm2)
- VWI Vessel Wall Area Segment Maximum (mm2)
- VWI Vessel Segment Wall Volume (mm3)
- VWI Local Normalized Wall Index (%)
- VWI Wall thickness Segment Average (mm)
- VWI Wall thickness Segment Maximum (mm)

Statistical Analyses (cross-sectional at visit 5)

Arterial stiffness and pulsatility will be dichotomized at the 75th percentile to indicate low (lower 75th percentile) vs. high (upper 25th percentile) arterial stiffness and/or pulsatility.

Descriptive statistics of demographic, lifestyle, clinical comorbidities, and intracranial measures will be examined by the dichotomized arterial stiffness/pulsatility measures and further stratified by race and gender.

Additional descriptive analyses will be performed to (1) examine the distributions of continuous values of cfPWV and cPP by number of plaques; and (2) examine the distributions of continuous values of cfPWV and cPP by degree of plaque stenosis (no detectable stenosis, <50% stenosis, 51%-70% stenosis, 71%-99% stenosis, and occlusion).

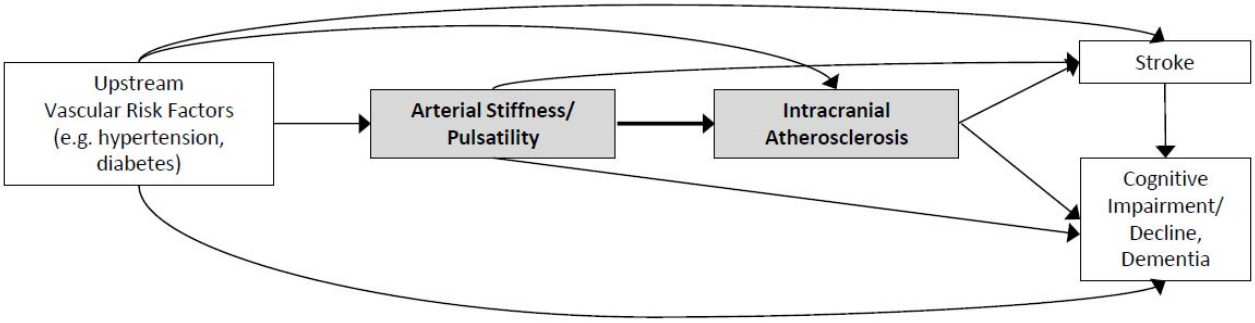
Logistic regression models will be used to quantify odds of (1) intracranial stenosis (> 50%) and (2) presence/absence of intracranial plaques (ICAD), by dichotomized cfPWV and cPP measures

Ordinal logistic regression will be used to quantify the association between arterial stiffness/pulsatility with (a) degree of arterial narrowing (no detectable stenosis, 50% stenosis, 51%–70% stenosis, 71%–99% stenosis, and occlusion), and (b) intracranial atherosclerotic plaque burden (i.e. number of plaques).

The following confounding variables will be included in the final model: age, sex, race, education, hypertension, diabetes, cholesterol, physical activity, smoking, body mass index

We will examine effect modification by age (<75/>75years), race and gender.

Figure 1. Conceptual Framework



Potential Modifiers of PWV-ICAD association: race, diabetes, hypertension, LDL, physical activity

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 ICTDER03 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

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?

____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)?

None found

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*)

___ 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. Agreed

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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