ARIC Manuscript Proposal #2446

PC Reviewed: 10/14/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority:**

1.a. Full Title:
MRI Measurements of Intracranial Atherosclerosis in the ARIC Neurocognitive Study: Methods, Reliability and Descriptive Statistics

1.b. Abbreviated Title (Length 26 characters):
MRI measurements of ICAD

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

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3. Timeline:

MRI vascular measurements in the ARICNCS cohort were completed by the end of June 2014. Manuscript preparation is expected to be accomplished by the end of September, 2014.

4. Rationale:

Intracranial atherosclerotic disease (ICAD) is a major cause of ischemic stroke worldwide [1, 2]. However, its prevalence may be underestimated due to the lack of an appropriate diagnostic tool to depict the intracranial vessel wall [3, 4]. The diagnosis of ICAD traditionally has depended on stenosis measurements by angiographic techniques [5], but ICAD may not necessarily cause proportional luminal narrowing as vessels are capable of compensatory dilatation (remodeling) to accommodate these changes, particularly early on [6, 7].

Black blood MR imaging (BBMRI) has emerged as an effective method to measure wall thickness and identify pathological features of extracranial vessels [8-10]. However, imaging intracranial vessel walls remains a technical challenge given the small size and tortuosity of these vessels. Recent development of a new 3D high-resolution MRI technique has made it possible to identify and characterize thickened intracranial vessel walls and this technique has gained much attention as more institutions have begun its implementation for clinical applications; however, the reliability of this test remains unknown with only repeat observer reproducibility estimates reported in small numbers of participants [11, 12]. The reliability of vessel wall thickness measurements by MRI generally depends on the thickness of the wall relative to scan resolution [13], with inadequate spatial resolution leading to grossly exaggerated thickness measurements [12]. This highlights the importance of understanding the reliability of imaging the relatively thin intracranial vessel wall using this technique.

In the ARIC-NCS study, we have implemented vascular sequences (i.e., 3D BBMRI and MRA) to measure intracranial vessel wall thickness and luminal narrowing. The objective of this study is to estimate the reliability of these measurements and report descriptive statistics representative of the general population.

5. Main Hypothesis/Study Questions:

Aims:

- To estimate reproducibility of MRI measurements in intracranial arteries.
  - Reliability of ICAD measurements will depend on location of the analyzed segment (i.e., more proximal segments will have better reliability because of thicker walls and larger lumens).
  - ICAD measurement variability will depend more on reader error than the MRI scan acquisition error for a given wall thickness (i.e., same vessel segment).

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).

MRI measurements:
The study will use data from 2,000 ARIC participants who underwent brain MRI to measure intracranial atherosclerosis in visit 5. The MRI exam was carried out on 3T MRI Siemens scanners. The MRI protocol consisted of a 3-dimensional time-of-flight MR angiogram through the Circle of Willis, centered to include the distal vertebral artery segments inferiorly and the middle cerebral artery branches superiorly. This was followed by a 3-dimensional high-isotropic resolution black blood MRI (BBMRI) scan oriented in a coronal plane and centered at the Circle of Willis. This vascular protocol was implemented at the end of the ARIC NCS brain MRI protocol, described separately.

Over the course of study, 102 participants were recruited for repeat MRI exams to estimate total MRI measurement error from both scan acquisition and reader variability. Participants were selected based on identification of at least one intracranial plaque on the baseline MRI scan, and an Image Quality score of either adequate or excellent. The median interval between repeat scans was 14 weeks. We will estimate the reader reliability based on the repeated interpretations by the same (n=100) and different (n=83) readers. We will estimate agreement and disagreement rates, intraclass correlation coefficient (ICC) and kappa statistics. The interval between readings by the same analyst is at least 90 days to minimize the influence of recall.

Inclusion/Exclusion criteria:
All exams with image quality and protocol adherence scores of adequate or excellent will be included in the analysis, and patients with poor or failed exams will be excluded.

Data Analysis:
All MRI images were interpreted by 6 certified analysts. Each analyst used picture archiving and communication system (PACS) software (Ultravisual; Emageon, Birmingham, Ala) for the qualitative analysis of the MRA and BBMRI scans. Using the PACS software, the BBMRI and MRA images were coregistered and reconstructed in both short and long axes relative to the flow direction for each vascular territory (RMCA, LMCA, RPCA, LPCA, ACA, Basilar, Vertebral, RICA, and LICA). For this analysis, the number of plaques identified for each territory will be recorded, with categorical stenosis recorded for the most stenotic plaque per territory using WASID criteria [14].

In addition, quantitative measurements of lumen size and stenosis from the MRA and wall/plaque size from the BBMRI were acquired using LAVA software (LAVA, Leiden University Medical Center, the Netherlands), which uses a deformable tubular model based on Non-Uniform Rational B-Splines (NURBS) surface modeling to contour each vessel segment. This technique provides semi-automated contour detection of the arterial lumen and performs an iterative linear regression fit of the lumen area over the entire segment. Standard vessel segments were measured (e.g., proximal Circle-of-

Willis branches such as M1 and basilar artery segments) over a fixed segment length, and the largest plaque identified for each vascular territory in the qualitative assessment was also measured.

Outcome and other variables of interest with specific reference to the time of their collection:

Variables of interest (include but are not limited to):
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 (i.e., zero to minimal luminal indentation, <50%, 50 to 70%, >70% and occlusion) (rmca_plaq_stenosis, lmca_plaq_stenosis, raca_plaq_stenosis, etc…)

Quantitative variables:

- MRA Area Degree of Stenosis (%)
- MRA Area Length of Stenosis (mm)
- MRA Area Obstruction (mm^2)
- MRA Diameter Degree of Stenosis (%)
- MRA Diameter Length of Stenosis (mm)
- MRA Diameter Obstruction (mm)
- VWI VesselWall Segment Average (mm2)
- VWI VesselWall Segment Maximum (mm2)
- VWI Segment Length (mm)
- VWI Vessel Segment Wall Volume (mm3)
- VWI Local Normalized Wall Index (%)
- VWI Wallthickness Segment Average (mm)
- VWI Wallthickness Segment Maximum (mm)

Descriptive Statistics (e.g., presence of plaques for race and gender):

- race and gender

Statistical analysis:
We will estimate agreement and disagreement rates, intraclass correlation coefficient (ICC) and kappa statistics. Bland-Altman plots will be employed to assess inter- and intra-reader variability. Prevalence of intracranial plaques will be estimated for race and gender using both qualitative and quantitative data. Race and gender comparisons will be made using chi-square analysis. A mixed effect model will be used to account for within-participant correlations. All analyses will be weighted according to the ARIC CNC study weighting scheme reflecting selection probabilities to obtain prevalence estimates representative of the ARIC cohort.

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)?
NA.

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
___ 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.

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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