ARIC Manuscript Proposal #2246

PC Reviewed: 10/8/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Pulse Wave Velocity and Retinal Microvascular Characteristics: the Atherosclerosis Risk in Communities (ARIC) Study-Neurocognitive Study (NCS)

b. Abbreviated Title (Length 26 characters): PWV and retinal findings

2. Writing Group:

Writing group members (**to invite and confirm**): Michelle L Snyder, A. Richey Sharrett, Vijay Nambi, Barbara E. Klein, Ronald Klein, Tien Y Wong, Priya Palta, Hirofumi Tanaka, others welcome

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

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3. Timeline: Analysis is to start on the current ARIC visit 5 data release as soon as the manuscript proposal is approved. We plan to complete the manuscript within three months from the final visit 5 data release.

4. Rationale:

Arterial stiffness is manifested by structural and functional changes to the vasculature that occur with age. Vascular risk factors are known to accelerate these physiological changes. Arterial stiffness is accompanied by high pulse pressure that is transmitted to the microvasculature and causes hypertrophy and vascular remodeling,[1] though such changes are not documented in the eye or brain.

Since the structure and properties of retinal arterioles may mimic that of cerebral arterioles, microvascular disease measured non-invasively by retinal fundus photography is of interest in the study of cerebrovascular disease[2]. Narrower retinal arterioles, larger retinal venules, and presence of arteriovenous nicking (AV nicking), focal arteriolar narrowing, and retinopathy were reported to be associated with cerebrovascular disease. In the Atherosclerosis Risk in Communities (ARIC) Study, retinal characteristics were associated with the risk of cognitive impairment,[3] white matter lesions,[4] and stroke.[4, 5] The association of retinal characteristics and heart disease, however, was not as consistent. In ARIC, whole narrower retinal arterioles were associated with the development of coronary heart disease (CHD) among women, it was not seem among men.[6] Retinal characteristics predicted 10-year cardiovascular mortality among participants 43 to 74 years old, but not in participants 75 to 84 years old in the Beaver Dam Eye Study.[7] A cross-sectional analysis of the Cardiovascular Health Study reported that retinopathy was associated with the prevalence of CHD, myocardial infarction, and coronary plaque; however, other retinal characteristics were not significantly associated with these outcomes. Many other cohort studies have shown prospective associations of retinal characteristics with incident CHD[8] and stroke.[9]

There is evidence suggesting that macrovascular arterial stiffness is associated with retinal vessel diameters in population-based studies. Aortic distensibility was associated with retinal arteriolar narrowing independent of factors considered to be confounding in the Multi-Ethnic Study of Atherosclerosis.[10] Similarly, Liao et al. reported that carotid arterial diameter change was directly associated with AVR, independent of covariates among 8,031 adults in the ARIC study.[11] This association did not differ by hypertensive status.

In Visit 5 of ARIC, pulse wave velocity (PWV) was measured using the OMRON VP-1000 device. PWV is considered to be a valid and reliable measure of arterial stiffness that predicts cardiovascular disease events and all-cause mortality in clinical and community based studies.[12] Carotid-femoral PWV (cfPWV) represents central arterial stiffness, and is the most commonly used measure in research studies. Additional measures available in ARIC are brachial-ankle PWV (baPWV) that represents both central and peripheral arterial stiffness, and segment-specific PWV representing central PWV (heart-femoral (hfPWV)) and peripheral PWV (femoral-ankle (faPWV)).

Evidence for an association between PWV and retinal characteristics is limited to studies evaluating diabetic retinopathy in participants with type 2 diabetes. In a cross-sectional analysis of 494 diabetic participants, Kim et al. showed that those with diabetic retinopathy had significantly higher hfPWV and baPWV, but not faPWV or

augmentation index compared to those without retinopathy.[13] After adjustment for confounding factors, only hfPWV was associated with diabetic retinopathy. Another cross-sectional analysis of 482 diabetic participants showed that retinopathy was associated with participants who had a cfPWV greater than 12 m/s (compared to less than 12 m/s) after adjusting for confounding factors.[14]

The association of PWV and retinal characteristics in a large population-based study is unknown, nor has an evaluation of segment-specific PWV and retinal characteristics been conducted. Based on 2,766 NCS Stage 2 examinees, the ARIC/NCS study will allow us to evaluate the association of cfPWV, baPWV, hfPWV, and faPWV with the retinal fundus microvasculature and with retinal microvasculature disease in a well characterized population of older African American and Caucasian men and women.

Understanding the association of arterial stiffness and retinal characteristics would generate hypotheses regarding the pathogenesis of cerebral abnormalities of vascular origin. If PWV is associated with retinal characteristics, it would suggest that macrovascular arterial stiffness may play a role in or be an indicator of microvascular changes, and would offer a tool to identify early manifestations of vascular change preceding end-organ damage.

5. Main Hypothesis/Study Questions:

We hypothesize that central and peripheral arterial stiffness (higher PWV) are associated with retinal vascular characteristics after adjustment for age, gender, and race. We posit that the association will be stronger among central measures of PWV (cfPWV and hfPWV) compared to peripheral measures (baPWV and faPWV). We will we explore effect modification by diabetes, hypertension, and smoking status (current smoking). Participants will be stratified by diabetes in the retinopathy analysis. The following are the aims of the study:

1. To quantify the cross-sectional association of PWV with retinal vascular characteristics (narrower central retinal arteriolar equivalent (CRAE), wider central retinal vein equivalent (CRVE) and presence of AV nicking, focal arteriolar narrowing, and retinopathy.

2. To test if the association of PWV and retinal vascular characteristics are modified by hypertension, diabetes, or smoking.

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: Cross-sectional analysis of participants at ARIC visit 5.

Inclusions: ARIC participants with PWV and retinal photography obtained at visit 5.

Exclusions: Missing information on PWV, retinal measures, or other covariates of interest, antihypertensive medication use, unreadable retinal photographs, not Caucasian

or African-American, African-Americans not from Jackson, MS or Forsyth County, NC, and participants with BMI≥40 kg/m^2. Also exclude participants with severe arrhythmias documented on their 12-lead ECG.

Variables of interest:

Retinal Characteristics

Digital retinal photographs were evaluated at the Ocular Epidemiology Reading Center (OERC) at the University of Wisconsin-Madison. CRAE and CRVE were calculated using a semiautomatic method used previously by ARIC.[15, 16] Retinal variables include the following: CRAE, CRVE, AV nicking, focal arteriolar narrowing, and retinopathy. We will also explore other less prevalent microvascular characteristics.

Pulse wave velocity (PWV)

PWV was measured by the Omron VP-1000 plus system (Colin Co., Ltd., Komaki, Japan) and the path length was calculated using the following formula: path length (cm) = carotid-femoral distance (cm) – (suprasternal notch – carotid distance (cm)). A minimum of two measurements were taken per participant and the last two usable measurements (i.e. non-zero values) were averaged.

PWV measurements include the following: carotid-femoral PWV (cfPWV), brachial-ankle PWV (baPWV), and segment-specific measures (heart-femoral (hfPWV) and femoral-ankle (faPWV)). We will also include the augmentation index (AIx) that is automatically calculated by dividing the augmented pressure by the pulse pressure.

Covariates

Covariates include field center, age, gender, race, hypertension (prevalent hypertension and/or blood pressure medication use), diabetes (prevalent and/or diabetic medication use), body mass index, C-reactive protein, systolic blood pressure, heart rate and current smoking.

Statistical Analysis:

We will present participant characteristics as means and standard deviations, medians and inter-quartile ranges (IQR), or as frequencies and percent, where appropriate. Conventional statistics will be used when data are normally distributed. If normality is a concern, non-parametric methods will be used. Analysis of variance (ANOVA) or independent sample t tests will be used to evaluate participant characteristics by retinal characteristics. Analysis of covariance (ANCOVA) will be used to estimate adjusted means of PWV by quartiles of CRAE and CRVE (adjusted for age, sex, field center).

The association of PWV and retinal characteristics will be examined by multivariable linear regression for CRAE and CRVE, and logistic regression analysis for the presence of AV nicking, focal arteriolar narrowing, and retinopathy. For these analyses, each PWV measure will be evaluated separately for the specific retinal measure. Model one will include field center, age and race. A second model will include variables in model one plus hypertension, diabetes and smoking. Possible first order interactions for gender, race, hypertension, diabetes, and smoking will be explored, and

the analyses will be stratified as necessary. As mentioned previously, participants will be stratified by diabetes in the retinopathy analysis. We will use a Bonferroni correction for all analyses to adjust p-values for multiple comparisons.

Sensitivity analyses: In a sensitivity analyses, we will investigate whether excluding participants with arrhythmias or adjusting for arrhythmias (reported use of antiarrhythmic or vasoactive medications per the ARIC medication survey use (MSR Item 33.g) and/or specific medication codes in the ARIC database) alters the strength of the associations.

Limitations: Some PWV and retinal measurements were not collected due to technical errors, participant factors and scheduling conflicts. Another issue to consider is that we should account for how participants were invited to stage 2 of ARIC NCS for the retinal fundus photography. Mortality or loss to follow-up before visit 5 could be associated with arterial stiffness and retinal characteristics, leading to potential for informative censoring/selection bias. Finally, the cross-sectional design limits our ability to determine causality.

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

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)?

MS#514 Association of arterial stiffness and retinal microvascular abnormalities (Liao D)

MS#1128 Relationship between carotid artery stiffness and age-related macular degeneration (Wong T)

MS#1234 10-year incidence, progression and regression of retinal vascular abnormalities and their relationship with vascular and inflammatory risk markers (Wong T)

MS# 1806 The association between arterial stiffness and incident heart failure and microvascular disease – an analysis from the ARIC study (Yang EY)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __X__ 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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