ARIC Manuscript Proposal #1970

PC Reviewed: 7/10/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Descriptive Epidemiology of Pulse Wave Velocity in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): ARIC Population Profile of PWV

2. Writing Group:

Writing group members: Michelle Meyer, Hirofumi Tanaka, Natalia Gouskova, David Aguilar, others welcome

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

First author: Michelle Meyer
Address: University of North Carolina at Chapel Hill
Bank of America Center
137 E. Franklin St., Suite 306
Chapel Hill, NC, USA 27514

Phone: 919-966-4596 Fax: 919-966-9800
E-mail: mlmeyer@unc.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
Name: Gerardo Heiss
Address: University of North Carolina at Chapel Hill
Bank of America Center
137 E. Franklin St., Suite 306
Chapel Hill, NC, USA 27514

Phone: 919-962-3253 Fax: 919-966-9800
E-mail: gerardo_heiss@unc.edu

3. Timeline: Analysis is to start on the initial, randomly sampled 50% of the ARIC Visit 5 records, as soon as released. We plan to complete the manuscript within one year from release of the data.

4. Rationale:

Pulse wave velocity (PWV) is a valid and reliable measure of arterial stiffness that predicts cardiovascular disease events and all-cause mortality in clinical and community based studies.[1] Carotid-femoral PWV (cfPWV) represents central arterial stiffness and is the most commonly used measure in research studies. However brachial-ankle PWV (baPWV) represents peripheral arterial stiffness and is commonly used in clinical settings in East Asian countries because of its ease of implementation. It is important that systematic studies are conducted in US populations to compare these two arterial segments and to determine the degree to which they measure the same arterial characteristics.

Given that the composition and function of the arteries vary by anatomical location,[2-6] the process of arterial stiffening might differ by arterial sites. Some reports suggest that PWV segments are not analogous as baPWV was not associated with known risk factors[7] and did not increase with age,[8, 9] an association well known with arterial stiffening and cfPWV.[10] On the other hand studies in Asian populations have shown that baPWV is comparable to cfPWV[11, 12] and correlated to CVD risk factors.[13, 14] The inconsistencies in the literature may be due in part to small sample sizes, various participant exclusions (excluding participants with hypertension, diabetes, dyslipidemia and obesity) and variations in the protocol for PWV.

Few studies of PWV have included both peripheral and central PWV despite the importance of both sites in measuring segment-specific arterial stiffness. The Atherosclerosis Risk in Communities (ARIC) Study cohort is community-based study which will allow us to evaluate the population distribution of central and peripheral arterial stiffness and its main correlates in a well characterized population of African American and white men and women.

The aim of this report is therefore to characterize central and peripheral arterial stiffness estimated from PWV in the ARIC Study at Visit 5 and to determine whether cfPWV and baPWV have similar associations with known correlates of PWV that include hemodynamic variables, e.g., age, race, gender and smoking. Understanding these relationships would generate hypotheses regarding its pathophysiological implications of segment-specific vascular stiffness.

5. Main Hypothesis/Study Questions:

1. Describe the distributions of central and peripheral arterial stiffness estimated from pulse wave velocity by age, gender and race.

2. Examine the similarities and differences in the associations of cfPWV and baPWV with hemodynamic variables, age, gender and race.

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.

Exposure:
Demographic variables: age, 10 year age groups, gender, race, hypertension (prevalent hypertension and/or blood pressure medication use) and study site.

Hemodynamic variables: resting heart rate, SBP, DBP, pulse pressure, mean arterial pressure.

Variables for a descriptive table of participant characteristics: body mass index, fasting glucose, triglycerides, total HDL-cholesterol and LDL-cholesterol.

Outcome: Carotid-femoral PWV (cfPWV) and brachial-ankle PWV (baPWV)

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.

Inclusions: All white and black ARIC participants with PWV data obtained at visit 5.

Exclusions: Missing information on PWV, blood pressure, and antihypertensive medication use or other covariates of interest; not white or African-American; and exclusions recommended by the ARIC ABI/PWV Working group: participants with BMI>=40, participants with major arrhythmias (based on ECG data), 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.

Statistical Analysis:

For Aim 1, we will present participant characteristics as means and standard deviations, as medians and inter-quartile ranges (IQR), or as frequencies and percent, where appropriate. If lack of normality is not a concern and transformation is not required then conventional statistics will be used. If normality is a concern we will use non-parametric methods.

We will show PWV between gender, race and 10 year age groups with cumulative frequency plots and statistical comparisons between groups will be tested using the Kolmogorov-Smirnov test. We will also assess the relationship between baPWV and cfPWV using the Spearman correlation coefficient.

Aim 2: We will examine whether the associations between hemodynamic variables and participant characteristics are similar for cfPWV and baPWV by using Spearman correlation coefficients and multivariable linear regression analysis adjusting for study site, age and HR. HR has been reported to be an important confounder in PWV analysis and is recommended to be accounted for in any analysis.[15, 16]

Independent variables for the regression analysis will include hemodynamic variables, age, gender and race. Variables with skewed distribution will be naturally log transformed for analysis. We will report standardized betas and R^2 values that represent the amount of variability in cfPWV and baPWV accounted for by variables in the model. Plots of baPWV versus cfPWV and predicted baPWV versus predicted cfPWV from the models will also be constructed. We will also evaluate whether there is a non-linear relationship between PWV and age (include age^2 terms) and investigate possible first order interactions between variables of interest and age, gender, race and hypertension. All analyses will be stratified as necessary.

Sensitivity analyses: In a sensitivity analyses, we will investigate whether excluding participants with hypertension (prevalent hypertension and/or antihypertensive medication use) or adjusting for hypertension in the regression analyses affects the strength of the associations.

Limitations:

Some PWV measurements were not collected due to technical errors, participant factors and scheduling conflicts. Despite adjusting for HR, some residual confounding cannot be excluded. 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)?

Since PWV is a new measurement in ARIC, the most related manuscript proposals are reports of arterial stiffness assessed by carotid distensibility. We have informed investigators that collaborations are welcome.

Previous reports include:
MS #723 Association of ethnicity and vascular stiffness
MS #003B The Distribution of Carotid Distensibility in the ARIC Population

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.

References

1. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: A systematic review and meta-analysis. *Journal of the American College of Cardiology*. 2010;55:1318-1327

2. Boutouyrie P, Laurent S, Benetos A, Girerd XJ, Hoeks AP, Safar ME. Opposing effects of ageing on distal and proximal large arteries in hypertensives. *Journal of hypertension. Supplement : official journal of the International Society of Hypertension*. 1992;10:S87-91
3. Lee RT, Kamm RD. Vascular mechanics for the cardiologist. *Journal of the American College of Cardiology*. 1994;23:1289-1295
4. Cavalcante JL, Lima JA, Redheuil A, Al-Mallah MH. Aortic stiffness: Current understanding and future directions. *Journal of the American College of Cardiology*. 2011;57:1511-1522
5. Kawasaki T, Sasayama S, Yagi S, Asakawa T, Hirai T. Non-invasive assessment of the age related changes in stiffness of major branches of the human arteries. *Cardiovascular research*. 1987;21:678-687
6. O'Rourke M. Mechanical principles in arterial disease. *Hypertension*. 1995;26:2-9
7. Tillin T, Chambers J, Malik I, Coady E, Byrd S, Mayet J, Wright AR, Kooner J, Shore A, Thom S, Chaturvedi N, Hughes A. Measurement of pulse wave velocity: Site matters. *Journal of hypertension*. 2007;25:383-389
8. O'Rourke MF, Staessen JA, Vlachopoulos C, Duprez D, Plante GE. Clinical applications of arterial stiffness; definitions and reference values. *American journal of hypertension*. 2002;15:426-444
9. Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, Vasan RS, Levy D. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: The framingham heart study. *Hypertension*. 2004;43:1239-1245
10. Cecelja M, Chowienczyk P. Dissociation of aortic pulse wave velocity with risk factors for cardiovascular disease other than hypertension: A systematic review. *Hypertension*. 2009;54:1328-1336
11. Sugawara J, Hayashi K, Yokoi T, Cortez-Cooper MY, DeVan AE, Anton MA, Tanaka H. Brachial-ankle pulse wave velocity: An index of central arterial stiffness? *Journal of human hypertension*. 2005;19:401-406
12. Tanaka H, Munakata M, Kawano Y, Ohishi M, Shoji T, Sugawara J, Tomiyama H, Yamashina A, Yasuda H, Sawayama T, Ozawa T. Comparison between carotid-femoral and brachial-ankle pulse wave velocity as measures of arterial stiffness. *Journal of hypertension*. 2009;27:2022-2027
13. Hung CS, Lin JW, Hsu CN, Chen HM, Tsai RY, Chien YF, Hwang JJ. Using brachial-ankle pulse wave velocity to associate arterial stiffness with cardiovascular risks. *Nutrition, Metabolism and Cardiovascular Diseases*. 2009;19:241-246
14. Tomiyama H, Yamashina A, Arai T, Hirose K, Koji Y, Chikamori T, Hori S, Yamamoto Y, Doba N, Hinohara S. Influences of age and gender on results of noninvasive brachial-ankle pulse wave velocity measurement--a survey of 12517 subjects. *Atherosclerosis*. 2003;166:303-309
15. Lantelme P, Mestre C, Lievre M, Gressard A, Milon H. Heart rate: An important confounder of pulse wave velocity assessment. *Hypertension*. 2002;39:1083-1087
16. Millasseau SC, Stewart AD, Patel SJ, Redwood SR, Chowienczyk PJ. Evaluation of carotid-femoral pulse wave velocity: Influence of timing algorithm and heart rate. *Hypertension*. 2005;45:222-226