

ARIC Manuscript Proposal #3272

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Priority: _____

1.a. Full Title: Associations between measures of regional pulse wave velocity: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Regional pulse wave velocity

2. Writing Group:

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

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3. Timeline: We plan to complete the manuscript(s) within one year from approval.

4. Rationale: Pulse wave velocity (PWV) is widely used in clinical and epidemiological studies to track cardiovascular health. The most widely used PWV measure is cfPWV. However, cfPWV can be challenging to measure and may be unsuitable for certain populations. For example, in patients who are at-risk, who have had an ischemic stroke, or more segments of the carotid arteries have advanced atherosclerosis.¹ This would complicate the interpretation of the cfPWV measures. Further, cfPWV is not consistent with the path of blood flow, and to adjust for this, an assumption is made about the timing of the pressure wave travelling in the opposite direction and this is used to adjust the measure accordingly.² There are potentially alternative regional measures which are simpler to conduct and/or can provide complimentary information. Our overall objective is to provide relevant information regarding correlations between different measures of arterial stiffness.

i. Heart-Femoral Pulse Wave Velocity: A promising alternative to cfPWV is heart-femoral PWV (hfPWV). The hfPWV, which measures the pulse wave between the heart and the femoral artery confers a number of potential advantages over cfPWV: i) it is simpler to conduct as the measurement is not dependent on palpating the carotid artery; and ii) the measurement path is consistent with the blood flow path. To date, few studies have utilized hfPWV,^{2,3} and the precision (between-day reliability) of hfPWV has not been reported.

ii. Aortic-Femoral Arterial Stiffness Gradient: The arterial vasculature progressively stiffens from the large aorta and large elastic arteries towards the peripheral muscular arteries. This gradient in arterial stiffness results in a gradual attenuation of forward pressure wave as it travels down the arterial tree to the microcirculation, where the pulsatility is minimal. However, of consequence to the attenuation of the forward pressure wave, the stiffness of the aortic and peripheral arterial segments change at varying rates with age and pathology. The gradient between aortic and peripheral arterial stiffness may be a useful marker of cardiovascular risk.

A recent study reported that an increased aortic-brachial arterial stiffness gradient (defined as the ratio of cfPWV and carotid-radial PWV (crPWV)) was a better predictor of all-cause mortality than cfPWV in dialysis patients.⁴ This observation was subsequently refuted in a study of community-dwellers (Framingham), which reported that the cfPWV/crPWV ratio and cfPWV equitably predicted CVD events.⁵ However, both of these studies utilized upper extremity arterial stiffness (crPWV) as their marker of peripheral arterial stiffness.

The lower extremities are more prone to athero- and arterio-sclerosis.⁶ Arterial stiffness in the legs can be characterized using femoral-ankle PWV (faPWV). No known studies have examined the relationship between faPWV/cfPWV ratio and cfPWV, or whether these two measures equally associate with standard cardiovascular disease risk factors.

iii. Femoral Pulse Wave Velocity vs. Ankle-Brachial Index: The ankle-brachial index (ABI) is commonly used to detect the presence of peripheral arterial disease, and to predict cardiovascular mortality. However, a recent review by the US Preventive Services Task Force concluded “there was no direct evidence and limited indirect evidence on the benefits of PAD screening with the ABI in unselected or asymptomatic populations.”⁷ The faPWV may be more closely associated with lower limb atherosclerosis and more strongly related to cardiovascular

disease risk factors. However, no known studies have examined the relationship between faPWV and ABI, or whether these two measures equally associate with standard cardiovascular disease risk factors.

Summary: The Atherosclerosis Risk in Communities (ARIC) Study cohort is a community-based study, with measures of PWV on over 6,000 older adults. Using data from ARIC Visit 5, we plan to address the following questions, which will allow us to generate hypotheses regarding the pathophysiological implications of segment-specific vascular stiffness.

5. Main Hypothesis/Study Questions:

- i. Are hfPWV and cfPWV correlated with one another?
 - a. Are correlations between PWV measures consistent across age, sex and race strata?
 - b. Do PWV measures equally associate with standard cardiovascular risk factors (e.g., SBP, HbA1c)?
 - c. What is the short-term repeatability of hfPWV and how does that compare with the repeatability observed for cfPWV?
- ii. Are cfPWV, faPWV and the faPWV/fPWV ratio correlated with one another?
 - a. Are correlations between these PWV measures consistent across age, sex and race strata?
 - b. Do the above PWV measures equally associate with standard cardiovascular risk factors (e.g., SBP, HbA1c)?
- iii. Are faPWV and ABI correlated with one another?
 - a. Are associations between PWV measures consistent across age, sex and race strata?
 - b. Do these measures equally associate with standard cardiovascular risk factors (e.g., SBP, HbA1c)?

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 data from ARIC visit 5.

Covariates: Demographic variables: age, 5 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.

Exposures/Outcomes: Carotid-femoral PWV (cfPWV) and heart-femoral PWV (hfPWV) PWV was measured by the Omron VP-1000 plus system (Omron Healthcare, Kyoto, 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

was 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. For repeatability analysis the subgroup (n=79) of visit 5 participants whom agreed to return for a repeat visit 4-8 weeks are the initial visit.

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 \geq 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 Measurement Comparison: 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 assess relationships between measures (cfPWV and hfPWV, cfPWV and fa-PWV ratio, and faPWV and ABI) using the Spearman correlation coefficients. We will examine whether the associations between hemodynamic variables and participant characteristics are similar for the measures by using Spearman correlation coefficients and multivariable linear regression analysis adjusting for study site-race, age, gender, and HR. 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 the measures accounted for by variables in the model. Plots (e.g., cfPWV versus hfPWV and predicted cfPWV versus predicted hfPWV) from the models will also be constructed. We will also evaluate whether there is a non-linear relationship between PWV and age (include age² terms) and investigate possible first order interactions between variables of interest and age, gender, race and hypertension. All analyses will be stratified as necessary.

Statistical Analysis for Repeatability of hfPWV: We will calculate intra-class correlation coefficient (ICC), standard error of measurement (SEM) and the minimal detectable change (MDC) with 95% confidence. The ICC will be calculated according to the formula: $SDb^2 / (SDb^2 + SDw^2)$, where SDb^2 and SDw^2 are the between and within-subject variance. In general, ICC values above 0.75 are considered to indicate excellent reproducibility. The SEM will be calculated according to the formula: $SD * \sqrt{(1-ICC)}$. The MDC will be calculated according to the formula: $1.96 * SEM * \sqrt{2}$. The MDC is defined as the critical difference in a parameter that must be exceeded between two sequential results for a statistically significant change to occur in an individual.

Sensitivity analyses: In 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 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? 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/search.php>

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)?

Meyer et al. (2016). Correlates of Segmental Pulse Wave Velocity in Older Adults: The Atherosclerosis Risk in Communities (ARIC) Study. American Journal of Hypertension 29(1): 114-122

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

11.b. If yes, is the proposal

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

References:

1. Grillo, A. *et al.* Influence of carotid atherosclerotic plaques on pulse wave assessment with arterial tonometry. *J. Hypertens.* **35**, 1609–1617 (2017).
2. Choo, J. *et al.* Regional pulse wave velocities and their cardiovascular risk factors among healthy middle-aged men: A cross-sectional population-based study. *BMC Cardiovasc. Disord.* **14**, 1–8 (2014).
3. Lee, S. W. *et al.* Relationship between brachial-ankle and heart-femoral pulse wave velocities and the rapid decline of kidney function. *Sci. Rep.* **8**, 1–9 (2018).
4. Fortier, C. *et al.* Aortic-Brachial Pulse Wave Velocity Ratio. *Hypertension* **69**, 96–101 (2017).
5. Niiranen, T. J. *et al.* Aortic-Brachial Arterial Stiffness Gradient and Cardiovascular Risk in the Community: The Framingham Heart Study. *Hypertens. (Dallas, Tex. 1979)* **69**, 1022–1028 (2017).
6. Thijssen, D. H. J. *et al.* Impact of inactivity and exercise on the vasculature in humans. *Eur. J. Appl. Physiol.* **108**, 845–875 (2010).
7. Guirguis-Blake, J. M., Evans, C. V., Redmond, N. & Lin, J. S. Screening for Peripheral Artery Disease Using the Ankle-Brachial Index. *JAMA* **320**, 184 (2018).