# ARIC Manuscript Proposal #2309

**PC Reviewed:  2/11/14**  **Status: <u>A</u>**  **Priority: <u>2</u>**

**SC Reviewed: _____**  **Status: _____**  **Priority: ____**

**1.a. Full Title:**  Repeatability of Pulse Wave Velocity in ARIC

  **b. Abbreviated Title (Length 26 characters)**: Repeatability of PWV

**2. Writing Group**:
    Writing group members: Michelle L Snyder, Hirofumi Tanaka, David Couper, Susan Cheng, Gerardo Heiss, Priya Palta, Mehul Patel, Ada Al Qunaibet, Anna Poon, Ricky Camplain, others welcome

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

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3.  **Timeline**: Analysis is to start as soon as approval is obtained. We plan to complete the manuscript within three months from data analysis.

4.  **Rationale**:
        Pulse wave velocity (PWV) is a non-invasive measure of arteriosclerosis that predicts cardiovascular disease events and all-cause mortality in clinical and community based studies.[1] ARIC Visit 5 included the measurement of PWV using an automated waveform analyzer (Colin VP-1000 Plus) that simultaneously captures central and peripheral measures of arterial stiffness.

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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)).

Despite the common use of PWV, the repeatability of the Colin VP-1000 Plus system used in ARIC has not been thoroughly examined in multi-center, population based studies. Previous studies have shown acceptable repeatability of PWV, but estimates were from different devices, such as the Sphygmocor or Complior,[2-4] and did not have segment-specific measures of PWV, Moreover, only one study reported an intra-class correlation coefficient for repeatability. Although the repeatability of PWV is similar across devices, slight variations exist due to the differences in how sensors capture the artery waveforms and how the software calculates PWV. An accurate assessment of the repeatability of the Colin VP-1000 Plus used to measure PWV in ARIC will aid in the analysis and interpretation of the measures.

The repeatability of cfPWV and carotid augmentation index (AIx) measured twice 3-5 minutes apart using the Colin VP-2000 has been reported.[5] The Pearson correlation coefficient and the coefficient of variation (CV) was 0.94 and 7% for cfPWV and 0.97 and 13% for AIx, respectively. This analysis was limited to repeat measurements taken on the same day, and the intra-class correlation coefficient or the absolute difference between measurements was not reported. The Pearson correlations and CVs reported do not measure repeatability or reliability. Repeatability of baPWV was assessed with Bland-Altman plots in a study consisting of a select group of participants with essential hypertension.[6] They found that mean baPWV measured with the Colin device did not significantly differ when taken 4 weeks apart (mean difference of 29 cm/s).

The ARIC Visit 5 examination included repeat measurements on a subset of participants (n=64) attending Stage I that will allow us to evaluate the repeatability of PWV measures. We will also evaluate the repeatability of parameters that were simultaneously measured with PWV. These include the augmentation index (AIx) calculated by dividing the augmented pressure by the pulse pressure, and the ankle brachial index (ABI) calculated by taking the ratio of the blood pressure in the lower legs to the blood pressure in the arms.

The aim of this report is to characterize the 4-8 week repeatability of PWV, AIx and ABI to guide the interpretation and reporting of these measures. Defining the repeatability of these measures will also inform the cross-sectional analyses of arterial stiffness, as well as the examination of long-term predictors of arterial stiffness in older adults.

**5. Main Hypothesis/Study Questions**:

1. Quantify the repeatability of PWV, AIx, and ABI.
2. Quantify the minimal detectable change and minimal detectable difference in PWV, AIx, and ABI for use in epidemiological studies.

**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 methodological limitations or challenges if present).**

**Study design:**

This repeatability analysis will include a subset of ARIC Visit 5 participants from Stage I that were invited to participate in the Repeatability Study. Field center staff asked the first eligible participant seen each month if he/she were willing to return 4-8 weeks later to repeat the study visit. If the participant was not interested, the staff recruited the next eligible and willing participant for the Repeatability Study. The Repeatability Study included 20 participants per field center (64 with PWV/ABI measurement; 11 Forsyth County, NC; 20 Jackson, MS; 14 Minneapolis, MN; 19 Washington County, MD). Trained technicians obtained PWV measurements following the same standardized ARIC PWV/ABI protocol and were blinded to the values from the original visit.

PWV was measured by the Omron Colin VP-1000 Plus system (Omron Co., Ltd., Komaki, Japan). At least two measurements were taken per participant per visit. Transit time is measured as the time delay between the proximal and distal 'foot' waveforms, i.e., the commencement of the sharp systolic upstroke. The time delays between right brachial and tibial arteries (Tba), between carotid and femoral arteries (cm), and between femoral and tibial arteries (Tfa) are obtained by the system. The path length from the carotid to the femoral artery (Dcf) is assessed over the surface of the body measured with a segmometer (Rosscraft, Surray, Canada), and calculated using the following formula: path length (Tba) = suprasternal notch to carotid distance (cm) – carotid to femoral distance (cm). The path lengths from the suprasternal notch to brachial artery (Dhb), from suprasternal notch to femur (Dhf), and from femur and ankle (Dfa) are calculated by the machine using the following height-based formulas:

Where $Dhb = (0.220 \times \text{height (cm)} - 2.07)$
$Dhf = (0.564 \times \text{height (cm)} - 18.4)$
$Dfa = (0.249 \times \text{height} + 30.7)$

$baPWV = (Dhf + Dfa - Dhb) / Tba$

**Outcome:** Repeatability estimates of PWV, AIx, and ABI.

Arterial stiffness measures include the following:
- Carotid-femoral PWV (cfPWV)
- Brachial-ankle PWV (baPWV)
- Femoral-ankle PWV (faPWV)
- Heart-femoral PWV (hfPWV)

Additional measures include the following:
- Augmentation Index (AIx)
- Ankle-brachial index (ABI)

**Other variables:** Age, gender, race, heart rate, systolic blood pressure, body mass index, smoking status, and use of antiarrhythmic or vasoactive medications.

**Inclusions:** All participants from the ARIC Visit 5 Repeatability Study that underwent the PWV/ABI measurement.

**Exclusions:** Missing information on PWV, AIx, ABI, and exclusions recommended by the ARIC ABI/PWV Working group: participants with BMI $\geq$ 40 kg/m$^2$ and participants with major arrhythmias (based on ECG data for MN code 8-1-3, 8-3-1 or 8-3-2).

**Statistical Analysis:**

We will present means and standard deviations (SD) of PWV, AIx and ABI for each measurement (PWV1 and PWV2 at the initial visit and then PWV3 and PWV4 four to eight weeks later). Measures with a skewed distribution will be expressed as medians and inter-quartile ranges and will be log transformed for the analysis. The average and absolute difference between pairs of measurements within-visit (PWV2 - PWV1 and PWV4 - PWV3) and between-visits will be calculated (PWV3 - PWV1 and PWV4 -PWV2).

We will use a nested random-effects analysis of variance model to parse the variance of the measures into between-participant ($\sigma^2_p$), between-visit ($\sigma^2_{bv}$), and within visit-components ($\sigma^2_{wv}$). We assume that the between-visit variation is the same for all participants and that the within-visit variation is the same for all visits and all participants, as previously described in the ECG repeatability analyses (ARIC MS# 894, 897, 2000, 2012). We will also account for the variability in heart rate by including models adjusted for heart rate.

To estimate the repeatability, the intra-class correlation coefficient (ICC) will be calculated by dividing the between-participant variance by the total variance [$\sigma^2_p/\sigma^2_{total} = \sigma^2_p/ \sigma^2_p+\sigma^2_{bv}+\sigma^2_{wv}$]. Measures with a skewed distribution will be log transformed to compute the ICC since the confidence interval is sensitive to departures from normality. We also calculate the standard error of measurement (SEM) as SEM = $\sqrt{(\sigma^2_{bv}+\sigma^2_{wv})}$. Since an ABI of <0.9 is used to indicate peripheral arterial disease, we will use the Kappa (K) statistic to evaluate agreement between visits [K = Po – Pe/1-Pe].

To examine the use of repeated measurements in study design development and interpretation of results, we will estimate changes in PWV, AIx and ABI based on the variance and sample size for one- and two-sample study designs. We will calculate the minimal detectable change with 95% confidence (MDC$_{95}$) between two time points for an individual that reflects true change above that of measurement error [MDC$_{95}$ = SEM*$\sqrt{2}$*1.96]. For a two-sample study design, we will calculate the minimal detectable difference (MDD) between two measurements as MDD = [($\sqrt{2}$*$\sigma^2_{total}$)/N]*($t_{\alpha(df)}+t_{\beta(df)}$), using the MDD as a percent of the grand mean.

*Sensitivity analysis:* In a sensitivity analysis, we will investigate whether excluding participants who reported current smoking or the 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 affects the repeatability estimates.

**Limitations:**

Arterial stiffness measurements are available at only two time points, thus our analysis is limited to repeatability 4-8 weeks later. Although the visits were conducted in the morning using a standardized protocol and study procedures designed to minimize measurement variability, it is possible that conditions were not exactly the same. We will evaluate possible variations in the protocol between visits by comparing path length, height, size of the cuffs, etc. Another limitation to consider is that we may not have the ability to estimate the variation due to

technician; however, the repeatability of cfPWV does not appear to be sensitive to technician variability using a Doppler method.[7]

**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)?**

We will invite authors from proposals using pulse wave velocity to collaborate on this manuscript proposal.

Also, related repeatability manuscripts are based on ECG measures from the ECG Repeatability Study.

Manuscript Proposal # 894 Repeatability of Heart Rate Variability Measures: The ECG Repeatability Study (published)

Manuscript Proposal # 897 Repeatability of the Spatial T Wave Axis Deviation Measures: The ECG Repeatability Study (published)

Manuscript Proposal #2000 Short-Term Repeatability of Electrocardiographic P Wave Indices and PR Interval" (published)

Manuscript Proposal #2012 Short-Term Repeatability of Electrocardiographic Tpeak-Tend Interval" (under peer-review)

**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

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