ARIC Manuscript Proposal #2722

PC Reviewed: 3/8/16	**Status: A**	**Priority: 2**
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1.a. Full Title: Repeatability of central and peripheral hemodynamic blood pressure measures: The ARIC Study.

1.b. Abbreviated Title (Length 26 characters): Repeatability of Central BP.

2. Writing Group: Susan Cheng, David Couper, Gerardo Heiss, Michelle Meyer, Hirofumi Tanaka, and Fran Yong (listed in alphabetical order).

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

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3. Timeline: We expect to complete the proposed manuscript within six months from the approval date. Please note that the proposed manuscript will be part of the first author's Master's paper, with guidance from Drs. Couper and Heiss.

4. Rationale: The hemodynamic properties of central aortic blood pressure (BP) have drawn attention for their association with small vessel diseases (SVD) and subclinical target organ damage (TOD) (Stone et al., 2015; Williams et al., 2006). Yet, the extent to which some of the central BP hemodynamic measures are reproducible in the general population is less well-known. We propose to characterize and quantify the measurement properties of central BP since they influence the ability to estimate unbiased associations between central BP and various traits and cardiovascular outcomes.

4.1. Central Blood Pressure in the Aorta and its Impact on Small Vessels: Central BP, particularly central systolic blood pressure (SBP), and (aortic) pulse pressure (PP) increase in the setting of age-related aortic wall remodeling and stiffening. In addition, a higher central BP alters the pulsating nature of the blood flow, transmitting the intensified (aortic) PP into small vessels in the brain and kidneys (Stone et al., 2015; Williams et al., 2006), with the potential to affect the progression of vascular cognitive impairment and chronic kidney disease as subclinical cardiovascular disease.

4.1.1. Central Systolic Blood Pressure and TOD: Arterial stiffening contributes to the progressive loss of the elasticity (or compliance) of the central ascending aorta; and an associated central pressure augmentation in late systole resulting from the backward-travelling pressure waves from the periphery (Steppan et al., 2011). As a result, central SBP increases whereas diastolic blood pressure (DBP) is maintained or decreases slightly, and PP widens. Although limited, studies have shown that central SBP and/or PP may be a better indicator(s) of subclinical damage in most organs and cardiovascular sequelae among individuals 50 years of age or older, compared to the conventional brachial BP. To illustrate, central SBP better reflects left ventricular hypertrophy and central PP better reflects atherosclerosis, compared to brachial BP (Agabiti-Rosei et al., 2007; Roman et al., 2007; Roman & Devereux, 2014 for cohort studies; Sharman et al., 2013 for RCT; and Kampus et al., 2011; McEniery et al., 2014; Williams et al., 2006 for anti-hypertensive drug trials).

4.1.2. Central Pulse Pressure and SVD: Pulse tends to propagate faster when central SBP and the internal pressure (due to stiffening) of arterial walls are higher, even if arteries have similar elasticity (Chirinos et al., 2014). Higher pulsatility in blood flow facilitates the transmission of intensified PP into the small vessels in the brain and kidneys, and contributes to cerebral microbleeds and impaired kidney function accordingly (O'Rourke et al., 2005; 2007). In other words, the pulse-induced damage increases the volume of white matter lesion in the brain; and progressive losses of glomerular filtration rate in the kidneys, contributing to the progression of vascular dementia and chronic kidney disease (Stone et al., 2015; Ohno et al., 2016). Yet, empirical evidence of the association between aortic PP and SVD based on population data is limited to date.

4.1.3. Brachial and Four-limb BPs: Different BP values in the arterial tree may reflect a different characteristic(s) of arterial remodeling (or stiffening), thus explaining different aspects of subclinical TOD and cardiovascular sequelae (McEniery et al., 2014; Sharman et al., 2008). To illustrate, SBP varies throughout the arterial tree (i.e., aorta, carotid, brachial, femoral, and peripheral) and BP categories, compared to the relatively uniform diastolic blood pressure (DBP). Central (aorta) SBP is usually lower than the corresponding peripheral values due to pulse wave augmentation (McEniery et al., 2014), whereas central and carotid SBP values are similar. Further, central SBP can differ between individuals with similar brachial SBP, or with similar peripheral SBP in the legs (McEniery et al., 2014; Sharman et al., 2008). Thus, improving our understanding of the association between a BP value over a specific artery (or measurement area) and pertinent TOD will be beneficial to CV risk assessment, rather than relying on the global cutoff-values. To assess and improve the quality of the results (i.e., unbiased estimation of the association), quantifying the measurement properties of central BP components provides useful information, such as their accuracy and repeatability.

4.2. Repeatability: Repeatability is obtained from repeated measures with the same device and protocol over a short time period (i.e., repeatability conditions). The variation of a measurement can be decomposed into between-participant variation (i.e., natural variation) and within-participants variation (i.e., measurement error). This can be expressed as

$$\sigma^2_{total} = \sigma^2_p + \sigma^2_b + \sigma^2_w \qquad [1]$$

where σ^2_{total} is the total variance of the observed BP values, σ^2_p is the component of variation due to the participants (or between-participants) (i.e., CVb), σ^2_b is the component of variation due to visit-time effects (or between-visits), and σ^2_w is the component of variation due to measurement error (i.e., component of variation within-visits, CVw). In this manner, repeatability is expressed as variance (i.e., mean and relative or absolute standard deviation, SD). Variance can be influenced by the distribution of the mean and a given sample size (i.e., methodological variability, CVc+m).Thus, here repeatability refers to within-person variability (CVw), between-person variability (CVb) and methodological variability (CVc+m) as the variance components of the measurement error that influence our ability to estimate unbiased associations.

4.2.1. Nested Data Structure: The dimensions of classical repeatability data are participants, measurement sessions, and repeated measures, where participants $i = 1,\ldots, N$, measurement session $j = 1,\ldots, N$, and k is the index for variation between repeated measures in each session. Accordingly, data have $i \times j \times k = N$ observations, and can be represented as in Table 1.

Table 1. Nested data structure of Repeatability (without technicians or with automated device)

Obs.	Participant ID	Session	Measurement	BP values
1	1	1	1	…
2	1	1	2	…
3	1	2	3	…
4	1	2	4	…
5	2	1	1	…
6	2	1	2	…
7	2	2	3	…
8	2	2	4	…
:	:	:	:	:
N	:	:	:	:

4.2.2. Empirical Model: The classical model labels that y_{ijk} denotes the value of the response variable observed at K^{th} repeated measures from each session j per each participant i, and this can be expressed as

$$y_{ijk} = u + P_i + V_{j(i)} + \varepsilon_{k(ij)} \qquad [2]$$

where u is an unknown constant, and $P_i, V_{j(i)}, \varepsilon_{k(ij)}$ are mutually uncorrelated random effects with means of zero and respective variances σ^2_p, σ^2_b, and σ^2_w. The main assumption of the model

is that $P_i, V_{j(i)}, \varepsilon_{k(ij)}$ are random variables, that is, uncorrelated with covariates (or both time-varying and -invariant covariates do not affect P_i under repeatability conditions (E [P_i | *covariates*] = 0). The three components of variance will be estimated from the ARIC Visit 5 'repeatability study' in which measurements were repeated according to the standardized ARIC examination protocol on 75 participant volunteers, 2-4 months after the initial examination visit during 2011-2013.

4.3. Objective: We propose to estimate the short-term (2-4 months) repeatability of central BP components and of the conventional brachial and peripheral BP components (i.e., conventional sitting brachial BP and simultaneous, supine four-limb BPs). Here BP components include SBP and PP. All measures use automated, non-invasive devices (Please see 6.3.1-2 outcome variables for measurement procedures).

5. Main Hypothesis/Study Questions/Specific Aims:

Aim 1: Estimate the within-session and short-term (2-4 months) repeatability of measures of central, brachial, and four-limb BP components, respectively, using automated non-invasive devices.

Aim 2: Estimate the minimal detectable change and minimal detectable difference for each of the study measures.

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).

6.1. Study Design: A secondary data analysis will be performed, using the blood pressure data from the ARIC Repeatability Study in 2011–2013 (N=300). The ARIC Repeatability Study was designed to compare two series of paired measurements taken on the same participants of 75. Measurements were performed twice, 5 minutes apart during the same visit, and then repeated at a second visit after 2-4 months. Trained and certified technicians obtained pertinent measurements using automated, non-invasive devices (i.e., the OMRON VP-1000 plus, and the OMRON HEM-907 XL for sitting blood pressure). The standardized ARIC Visit 5 protocol was used each time. Specific recruitment process can be found elsewhere (Meyer et al., 2015).

6.2. Inclusion/Exclusion criteria: All eligible participants are the members of the ARIC Visit 5 examination, who are free of major cardiovascular conditions and proportionally distributed over the four ARIC field centers.

6.3. Outcome variables: Three types of BP component measures will be addressed. The primary one are the central BP components (i.e., cSBP and cPP). The two other types of BP component measures are the conventional brachial BP (bBP) over the upper arm in the seated position (i.e., bSBP and bPP); and four-limb BP measured simultaneously in both arms and ankles by the OMRON VP-1000 plus (i.e., $_{\text{right-arm}}$SBP, $_{\text{left-arm}}$SBP, $_{\text{right-ankle}}$SBP, $_{\text{left-ankle}}$SBP, $_{\text{right-arm}}$PP, $_{\text{left-arm}}$PP, $_{\text{right-ankle}}$PP, and $_{\text{left-ankle}}$PP).

6.3.1. Central BP measurement: Central SBP was measured in the supine position using a tonometry sensor in the automated, non-invasive OMRON VP-1000 plus device over the

precordial area. Central PP will be derived from central SBP minus right brachial DBP as an estimate of the central DBP (i.e., cPP = cSBP – right bDBP). Right bDBP will be used as a surrogate of cDBP because DBP values remains largely uniform throughout the arterial tree (McEniery et al., 2014).

6.3.2. Brachial BP and four-limb BP measurement: Conventional bBP was measured in the seated position by an automated oscillometric sphygmomanometer (the OMRON HEM-907 XL device), after 5 minutes of rest, using a cuff size appropriate to the upper arm circumference (i.e., bPP = bSBP – bDBP). Four-limb BPs were measured with the automated OMRON VP-1000 device in the supine position over both arms and ankles simultaneously.

6.4. Other variables: Variables that may affect the repeatability of the study measures will be selected a priori. They include age, gender, black/white race, current cardiovascular morbidity, heart rate (Lantelme et al., 2002; Wilkinson et al., 2002), smoking status, height (Reeve et al., 2014), weight, and a measure of obesity.

6.5. Analysis Plan: Nested random-effects modeling will be used to test our specific aims, as an established analytical approach to compare two series of paired measurements (Littell et al., 2006). It allows us to decompose the total variance into the three components of variance (i.e., between-participant variance, and each of between- and within-visit variance on the same participants). Repeatability of the study measures will be presented in the following analytic steps according to the recommendations of Bland and Altman (1986): intra-class correlation coefficients (ICC), coefficient of variation (COV), and agreement test visualized by Bland-Altman plot (i.e., mean-difference plot). In addition, repeatability will be presented as minimal detectable change and difference (MDC and MDD) as we discussed in section 4.2. The conventional two-sided P-value of 0.05 will be used; and all statistical analyses will be performed using SAS 9.4 (Cary, North Carolina).

6.5.1. Univariate analysis: Univariate analyses will be performed for all variables. Out-of-range values or outlier values will be checked for errors. In addition, this initial analysis will serve the purpose of describing the participants' characteristics at the baseline (or 1st visit), identifying skewed variables that need transformation.

6.5.2. Mean Difference and Paired *t*-test (Aim 1): To test whether there is a difference in repeated measures within-and between-visits, respectively, mean values and standard deviations (±SD) of each measurement will be summarized with paired t-test. Each measure will be compared between the first and second measures taken during the first visit (i.e., within-visit comparison). Then each of the two measures taken during the first visit will be compared to the repeated measures taken on the second visit (i.e., between-visit comparison) (Meyer et al., 2015). Average, absolute and relative mean differences within-and between-visit comparisons, respectively will be reported.

6.5.3. ICC (Aim 1): To estimate the similarity of measured values within-and between-participants, respectively, ICC (or reliability coefficient) for pairs of each measure at the same visit (i.e., within-visit ICC) will be calculated. Then, the average ICC for each measured value at the first visit, paired with that of each measured value at the second visit will be calculated (i.e., between-visit ICC). For within-visit ICC, ICC can be expressed as the ratio of the between-person variance to the total variance [3]. It can be interpreted as the proportion of the total

variance not attributable to within-participant variance (i.e., random measurement error); and will inform about the repeatability of a single measurement for a single participant. For between-visit ICC, the average ICC can be expressed as the ratio of between-visit variance over total variance [4]. It will inform about the repeatability of the mean of repeated measures over 2 visits. The calculated ICCs with 95%CI will be reported. ICC ranges from 0 to 1; and the standard cut-point (ICCs > 0.75) will be used as a reasonable repeatability. If measured BP values are not normally distributed (i.e., violation of the assumption of 95% CIs), we will use the standard bootstrap method to calculate 95% CIs.

$$\text{ICC} = \frac{\sigma_p^2}{\sigma_{total}^2} = \frac{\sigma_p^2}{\sigma_p^2+\sigma_b^2+\sigma_w^2.} \quad [3]$$

$$\text{ICC}_{\text{average}} = \frac{\sigma_b^2}{\sigma_{total}^2} \quad [4]$$

6.5.4. COV (Aim 1): To compare the relative size of variation to the mean value of each of the study measures, relative standard deviation or coefficient of variance (COV) will be calculated. COV shows a standardized measure of variation and typically is constructed as a ratio of SD to the mean [5]. Given the observation *N*, COV (or relative SD) would be more intuitive than measures of absolute dispersion. Estimated COV will be presented with ICC.

$$\text{COV} = \frac{SD}{mean} \times 100 \quad [5]$$

6.5.5. Bland-Altman plot (Aim 1): To assess agreement (or degree of heteroscedasticity) of repeated measures within-participants, Bland-Altman plots (or mean-difference plots) will be used to visualize the correlation between the absolute different from 1st to 2nd test (i.e., test – retest) and the magnitude of the grant mean of the two measures, with 95% limits of agreement. The 95% limits of agreement will be calculated as [6]. No significant will infer agreement in repeated measurements.

95% limits of agreement = Δ Mean ± 1.96 x SD of Δ Mean [6]

6.5.6. Minimal detectable change and difference (Aim 2): To estimate whether the difference of measured values is a result of true change, not measurement error, MDC with 95%CI (MDC_{95}) will be calculated within-participants (i.e., one-sample study design) and MDD with 95% CI (MDD_{95}) between-participants (i.e., two-sample study design). They can be expressed as

$$\text{MDC}_{95} = SEM * \sqrt{2} * 1.96 \quad [7]$$

where 1.96 is the two-sided tabled z value for the 95% CI and $\sqrt{2}$ is used to account for the variance of two measurements. MDC refers to the smallest amount of change that is likely to reflect a true change rather than measurement error (i.e., representing the magnitude of change necessary to exceed the measurement error of two repeated measures at a specified CI). MDC can extend to measurement over times and/or two-sample study such as minimal detectable difference (MDD) [8] to estimate sample size or feasibility of a future study.

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$$\text{MDD}_{95} = [(\sqrt{2} * \sigma_T^2)/\text{N}]*(\text{T}\alpha(\text{df})+\text{T}\beta(\text{df})) \quad [8]$$

6.6. Potential limitations: Two potential limitations may be considered. First, blood pressure varies by gender and age, yet the sample size of the study data does not allow estimations of gender- and/or age-specific repeatability. Thus the inference of the results may be limited to the overall population. Second, we will use brachial DBP to approximate central PP due to the unavailability of central DBP. Although this is not optimal and may influence the accuracy of the measured central PP values, we assume that the influence would not be significant because DBP values are relatively uniform throughout the arterial tree as we describe in the rationale (please see section 4.1.3). Finally, it may be important to note that the repeatability data for this proposed manuscript used automated devices to measure PP. Thus the measured values should not be greatly influenced by technicians (observers).

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)?

- Manuscript Proposal #2309:
  "Repeatability of Central and Peripheral Pulse Wave Velocity Measures: The Atherosclerosis Risk in Communities Study" (published)

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.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __ X __ No.

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