ARIC Manuscript Proposal #2167

PC Reviewed: 7/9/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Ipsi- and Contra-lateral differences in arterial blood pressure in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): BP differences in ARIC

2. Writing Group:

Hirofumi Tanaka, Natalia Gouskova, Michelle Meyer, Kimberley Ring, Vijay Nambi, Gerardo Heiss, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _HT_

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3. Timeline: Analysis is to begin Summer 2013. We plan to complete the manuscript within one year from release of the data.

4. Rationale:

Blood pressure is a prototypical quantitative trait known to be variable. It fluctuates beat-by-beat basis and from daytime to nighttime. Blood pressure can be substantially different in each limb that blood pressure is measured. Several epidemiological studies reported that a large inter-arm difference in brachial systolic blood pressure (SBP) (i.e.,

≥10 or ≥15 mmHg) is associated with elevated cardiovascular events and mortality [1, 2]. Pathophysiology linking contralateral differences in brachial SBP and cardiovascular mortality is unknown but subclinical and/or clinical vascular disease affecting one side of the body (e.g., coarctation, subclavian artery stenosis) has been suggested [3]. Physiological factors such as arterial stiffness could also play a role as SBP is strongly influenced by the stiffening of arteries [4]. Indeed, individual variabilities in contralateral differences in pulse wave velocity have been reported [5]. However, there is no information available to address this question. Moreover, it is not known if such contralateral differences in SBP also occur in ankle blood pressure and whether differences in ankle blood pressure are associated with those in brachial blood pressure. Considering the evidence that arterial wave reflection is a primary mechanism responsible for augmenting SBP and that the lower body is believed to be the important site of wave reflection [6], contralateral differences in SBP, if any, may be influenced by the stiffness of arteries to a greater extent in the ankle than in the arm. However, such issue has not been addressed.

Similar to contralateral blood pressure differences, a large ipsilateral difference in blood pressure (ie, differences in SBP between the brachial artery and ankle on the same side of the body) is taken as a pathological manifestation of peripheral artery disease (if it is ≤0.9) or calcification of lower limb arteries (if it is >1.5) [7]. However, values that fall between 0.9 and 1.5 have received much less attention. Given the larger contribution of the lower body to wave reflection and impedance mismatch, it is plausible that a larger ipsilateral differences in blood pressure within the range of 0.9 to 1.5 may be associated with vascular dysfunction or more specifically arterial stiffness.

Accordingly, the aims of this study were to assess the prevalence of brachial and ankle contralateral SBP differences in a sample of community dwelling older adults, and to determine whether this difference is associated with arterial stiffness.

5. Main Hypothesis/Study Questions:

1. Describe the prevalence of contralateral differences in SBP both in the brachial and ankle (posterior tibialis) arteries.

2. Determine the associations between arterial stiffness and contralateral as well as ipsilateral SBP differences.

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

Exposure:

Demographic variables: age, gender (sex), race, and hypertension (prevalent hypertension and/or blood pressure medication use).

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

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

Outcome: Arterial stiffness measures including carotid-femoral PWV (cfPWV), brachial-ankle PWV (baPWV), and carotid artery augmentation index; contralateral and ipsilateral differences in systolic blood pressure.

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.

A major advantage of this system for the research question addressed is that blood pressure was measured in all 4 limbs simultaneously [8]. Thus, beat-by-beat differences in blood pressure between limbs are considered a minimum. Contralateral differences in brachial blood pressure will be defined as right-left differences of SBP >10 or >15 mmHg. Since there are no published data on contralateral differences in ankle blood pressure or ipsilateral differences in blood pressure, we will use SBP >10 or >15 mmHg differences initially. Smaller and/or larger differences in blood pressure will be considered depending on the preliminary data analyses.

Inclusions: All 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; and exclusions recommended by the ARIC ABI/PWV Working group: participants with BMI $\geq$40, participants with major arrhythmias (based on ECG data), participants with ABI <0.9, 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:

Participant characteristics will be reported 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 examine the associations between arterial stiffness and inter-limb differences in systolic blood pressure by using multivariable linear regression analysis. 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 arterial stiffness and inter-limb differences in systolic blood pressure accounted for by variables in the model.

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.

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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