1.a. Full Title:

Association of central versus peripheral hemodynamic indices with target organ damage in older adults: The ARIC Study

b. Abbreviated Title (Length 26 characters): CBP as a marker of TOD

2. Writing Group:
Susan Cheng, Rebecca F. Gottesman, Gerardo Heiss (invited), Kunihiro Matsushita (invited), Hirofumi Tanaka, B. Gwen Windham, 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: Anticipate manuscript completion within 9 months from the approval date.

4. Rationale:
4.1. Goal: We propose to assess association of central versus peripheral hemodynamic indices with target organ damage (TOD) among adults aged 65 and more.

4.2. Background: The European guideline recommends to assess target organ damage (TOD) among individuals with suspected and established hypertension.1 Uncontrolled TOD or symptomatic small vessel disease (SVD) in the heart, kidneys, and brain is most likely to become irreversible conditions (e.g., refractory heart failure, end stage of renal disease, and dementia), affecting the rapidly growing population group of older adults.
Derived central hemodynamic indices – cSBP, cPP and cAIx - are potentially promising markers for TOD among adults, showing stronger association than standard brachial pressure. In brief, central aortic pressure more accurately represents pressure load imposed on the left ventricle and coronary and cerebral vasculatures than brachial pressure. The low-impedance renal and cerebral micro-vasculatures are easily damaged by intensified pulsatile pressure (attributable to late systolic flow augmentation in the aorta). Carotid or aortic augmentation index (cAIx) (as a measure of wave reflection) represents decreasing left ventricular contractility after around age 60 years; and is considered a comprehensive measure of both the aortic pressure and arterial stiffness.

Up-to-date, most published data address macro-circulation such as left ventricle structure abnormalities and atherosclerosis (e.g., ankle-brachial index and carotid intima-media thickness). Few data report alterations in the micro-circulation of the heart-kidneys-brain, where they share similar vascular beds. The extent to which each of the central hemodynamic indices is associated with TOD in these vital organs is less well established.

In addition, most published data document central BP with younger adults as a single population. Given changing demographics and adverse impact of diabetes (or endothelial dysfunction) on renal and cerebral micro-vasculatures, it is important to expand the prior efforts to older adults aged 65 and more; and further by risk categories (e.g., (a) stages of isolated systolic hypertension (ISH); (b) cross-classification of ISH and diabetes: non-diabetic normotensive, diabetic normotensive, non-diabetic ISH, diabetic ISH; (c) standard hypertension classification).

Further, it is not well known whether central hemodynamic indices can distinguish between those with and without TOD as closely as the corresponding gold standard. We previously demonstrated repeatability of central hemodynamic indices available in the ARIC Visit 5 data. Evaluation of their performance [in terms of sensitivity and specificity; and an optimal cut-off value(s)] will provide additional insight into potential utility of central hemodynamic indices as a marker for TOD outside of the vascular laboratory.

5. Aims/Main Hypothesis/Study Questions:

We propose 3 aims to address the gaps mentioned in section 4.

Aim 1: Describe distributions of central hemodynamic indices in older adults, overall and by ISH/HTN and diabetes.

Aim 2: Estimate the magnitude of independent association of central hemodynamic parameters with TOD in the vital organs.

Aim 3: Assess performance of central hemodynamic indices in discriminating TOD against the corresponding gold standard.
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. Design and Study Population: Retrospective, cross-sectional analysis with the ARIC Visit 5 data, concurrent with ARIC Echo and ARIC-NCS MRI data (Table 1). All ARIC participants with the central and brachial hemodynamic indices or TOD measures will be included, except for participants of races other than black or white.

Table 1. Source of data by study aim

<table>
<thead>
<tr>
<th>ARIC Visit 5</th>
<th>Aim 1</th>
<th>Aim 2 and 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main Cohort/BP</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Echo</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>MRI (from ARIC-NCS)</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

6.2. Central Hemodynamic Indices: Derived cSBP, cPP, and cAIx will be used either as a continuous or categorical variable (according to standard BP classification as in other studies2). Details of measurement procedures have been published.9,10

6.3. Outcomes: Indicators of TOD for this study are listed in Table 2 and will be used as a binary, categorical or continuous variable as in published ARIC reports, where members in this writing group participated.11-15

Table 2. Indicators of TOD in the vital organs

<table>
<thead>
<tr>
<th>Heart1,12</th>
<th>Threshold or Range</th>
</tr>
</thead>
</table>
| Left ventricular hypertrophy (LVH) | LVMI/BSA >115 g/m² in men  
LVMI/BSA >95 g/m² in women |
| Left ventricular mass index (LVMI)a | Continuous variable of LVMI/BSA |
| N-terminal pro-brain natriuretic peptide (NT-proBNP) | The highest quartile or, >125 pg/ml |
| High-sensitivity cardiac troponin (hs-cTnT) | The highest quartile or, ≥ 0.014 µg/L |

<table>
<thead>
<tr>
<th>Brain13</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>White matter hyperintensities (WMHs)</td>
<td>Total WMH Volume (range: 0-9)</td>
</tr>
<tr>
<td>Infarcts (defined as infarct burden) b</td>
<td>Ordinal variable (range: 0-3)</td>
</tr>
<tr>
<td>Microbleeds (in subcortical areas)</td>
<td>Number of Microbleeds (range: 0-10)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Kidneys14,15</th>
<th></th>
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</thead>
</table>
| Albuminuric | UACRc ≥30 mg/g or,  
UACR ≥3.9 mg/g for men  
UACR ≥7.5 mg/g for women |
| estimated glomerular filtration rate (eGFR) | eGFR < 60 ml/min per 1.73 m² |

a. LV mass is indexed to body surface area (LVMI/BSA)  
b. Infarct burden variable is created on the ordinal scale by the ARIC-NCS MRI investigators.  
c. UACR refers to urine albumin-to-creatinine ratio
6.4. Other variables to be analyzed: Standard brachial SBP, PP, and AIx will be used for comparison. Known risk factors will include age, gender, race, smoking status, BMI, abdominal circumference, heart rate, HDL and LDL cholesterol level, triglycerides, antihypertensive medication use, diabetes, field center and education level.

6.5. Analysis Plan:
6.5.1. Aim 1: To describe distributions of central hemodynamic indices, we will present summary statistics overall and by the proposed risk categories: ISH/HTN and diabetes. The distributions may be further stratified by gender, depending on available sample sizes.

6.5.2. Aim 2: To estimate independent association of central hemodynamic indices with TOD, separate multivariate modeling will be fit adjusting for known risk factors (i.e., linear, binary or ordinal logistic modeling based on the nature of an outcome/TOD indicator). Independent association will be gauged by p-value. The same modeling procedures will apply to brachial hemodynamic indices for comparison. In addition, as long as sample size is allowable for analysis, we will conduct subgroup analysis based on the proposed risk categories.

When fitting multivariate models, we will exclude the following using ARIC definition of adjudicated events.

a. For the heart, those with a history of heart failure (HF) or myocardial infarction/coronary artery disease will be excluded.

b. For the kidneys, those with a history of end stage of renal disease will be excluded.

c. For the brain, those with a history of stroke or dementia will be excluded.

Prior to modeling, univariate analyses will be performed for all variables, identifying skewed variables that need transformation; and multicollinearity. If there are non-ignorable missing data in TOD/outcome variables, we will impute using the Markov Chain Monte Carlo method.

6.5.3. Aim 3: To evaluate performance of central versus brachial hemodynamic measures that distinguishes between those with and without TOD, receiver-operating characteristic (ROC) analysis will tabulate optimal cut-off value(s), area under curve (AUC; range 0.5-1), sensitivity (SE), specificity (SF), positive and negative predictive values, likelihood ratios and 95% confidence intervals. AUC will be displayed graphically as well (i.e., plot of SE against 1-SF).

The conventional two-sided P-value of 0.05 will be used and statistical analyses will be performed using SAS 9.4 (Cary, North Carolina).

6.6. Potential limitations: Derived central hemodynamic indices need to be calibrated using brachial pressure. Additionally, the difference between augmented central and brachial pressures become smaller with advancing age. It may be possible that the magnitude of association of central versus brachial pressure with TOD may not be quite distinct. In case we will additionally present correlation or partial correlation. Despite the challenge, the expected results will add to the growing evidence on potential utility of central hemodynamic indices as a marker for TOD in (largely understudied) older adults; and probably be the first report on association with TOD in the brain in the setting of population studies.

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 _____ 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

 _____ 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)?

First author consulted with Dr. Gerardo Heiss (leader of BP working group) in early May 2017 regarding her follow-up study topics on MS # 2722 (published); and she also reviewed the completed, assigned and unassigned topics that the PWV/ABI working group has lined up.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _____ Yes _____ 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 \url{http://publicaccess.nih.gov/} are posted in \url{http://www.cscce.unc.edu/aric/index.php}, under Publications, Policies & Forms. \url{http://publicaccess.nih.gov/submit_process_journals.htm} shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using 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 \url{pingping_wu@unc.edu}. I will be using CMS data in my manuscript \underline{Yes} \underline{X} \underline{No}. 
REFERENCE

1. Mancia, R. Fagard, Narkiewicz K et al., ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC), Eur. Heart J. 2013; 34(28); 2159-2219.


