

ARIC Manuscript Proposal #2721

PC Reviewed: 3/8/16
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.

a. Full Title: Arterial stiffness and subclinical cardiac damage and overload in older adults: The Atherosclerosis Risk in Communities (ARIC) Study.

b. Abbreviated Title (Length 26 characters): PWV & cardiac biomarkers

2. Writing Group:

Writing group members: Shuiqing Liu, Aozhou Wu, Michelle Meyer, Susan Cheng, Ron C. Hoogeveen, Christie M. Ballantyne, Hirofumi Tanaka, Gerardo Heiss, Elizabeth Selvin, Kunihiro Matsushita

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline: Analysis will begin following proposal approval. As all data for this project are available, analysis and manuscript preparation will be completed within 6 months after receiving proposal approval.

4. Rationale:

Arterial stiffness indicates increased rigidity and decreased elasticity of the arterial wall in response to pressure changes¹⁻³ and is considered as an important characteristic of aging process.⁴ When arteries are stiff (less compliant), left ventricular (LV) end-systolic pressure increases and therefore the heart requires increased energy to ensure the adequate blood output to the body.^{4,5} Over time, this leads to LV hypertrophy, concentric remodeling,⁶ and diastolic dysfunction.^{5,7} Indeed, parameters of arterial stiffness (particularly carotid-femoral pulse wave velocity [cfPWV] reflecting central arterial stiffness) are shown to independently predict cardiovascular disease (CVD).⁸⁻¹¹

Indicating the involvement of arterial stiffness at early stage of pathophysiological process to cardiac disease, several studies have demonstrated the association between arterial stiffness and cardiac biomarkers including natriuretic peptides (BNP)¹²⁻¹⁷ and cardiac troponin T (TnT),¹⁸⁻²⁰ among those without clinical cardiac disease. However, only one of these studies account for parameters of cardiac structure and function,¹⁵ leaving uncertainty regarding whether arterial stiffness contributes to cardiac damage or overload before the manifestation of LV hypertrophy or remodeling. Also, most of these studies focused on either TnT¹⁸⁻²⁰ or natriuretic peptides,¹²⁻¹⁷ but not both, investigated clinically selected populations^{14-16,19,20} (e.g., hypertension,^{15,16,19} and chronic kidney disease^{14,20}), and included a small number of participants (often n < 1000).^{13-16,19,20} In addition, only a few of them investigated arterial stiffness in multiple vascular beds.^{12,16}

Therefore, we aim to explore the associations of segment-specific PWVs, with biomarkers of both cardiac damage (TnT) and overload (natriuretic peptide) in a large sample of community-dwelling older adults in the ARIC Study.

5. Main Hypothesis/Study Questions:

- a. PWVs are associated with high-sensitivity TnT (hs-TnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), independently of traditional cardiovascular risk factors.
- b. PWVs are associated with hs-TnT and NT-proBNP, even when we account for LV hypertrophy, concentric remodeling, and diastolic dysfunction.
- c. PWVs reflecting central arterial stiffness demonstrate stronger associations with hs-TnT and NT-proBNP compared to PWVs representing peripheral arterial stiffness.

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 study using the ARIC population at visit 5

Inclusions:

-All black and white ARIC subjects who have data on PWV, hs-TnT and NT-proBNP at visit 5 and do not meet the exclusion criteria below

Exclusions:

- Ethnicity other than black or white
- Missing data on PWV, hs-TnT and NT-proBNP
- Those with a history of cardiac disease (coronary heart disease and heart failure)
- Per recommendations from the ARIC PWV working group, those with concerning reliability of PWVs: severely reduced ejection fraction (<30%), overt arrhythmia including atrial fibrillation, morbidly obese (body mass index (BMI) ≥ 40 kg/m²), history of aortic or peripheral revascularization, aortic aneurysm, aortic stenosis, and PWV values greater than 3 SD away from the mean.

Exposure (independent variables):

- Arterial stiffness measures
 - Arterial stiffness will be measured by PWVs at visit 5 including carotid-femoral (cf) PWV reflecting central arterial stiffness, femoral-ankle (fa) PWV reflecting peripheral arterial stiffness, and brachial-ankle (ba) and heart-ankle (ha) PWVs reflecting both central and peripheral stiffness.

Outcome (dependent variables):

- hs-TnT will be considered as a measure of subclinical cardiac damage
- NT-proBNP will be considered as a measure of cardiac overload

Other variables of interest and covariates:

- Sociodemographics: age, race, gender, education level, and center
- Physical information: body mass index, waist circumference, blood pressure, and heart rate
- Lifestyle: smoking status, alcohol habit, and physical activity
- Comorbidities: diabetes, hypertension, dyslipidemia (including lipid profile), kidney function and kidney damage, inflammation (high-sensitivity C-reactive protein), LV hypertrophy, concentric remodeling (accounting for relative wall thickness), and diastolic dysfunction (left atrial volume index)

Statistical Analysis Plan:

The primary analysis will use linear regression models to quantify the association between arterial stiffness measures and cardiac damage and overload. PWVs will be treated as continuous variables with splines and categorical variables based on quantiles (e.g., quartiles). We will test several models to assess the influence of potential confounders. Model 1 will be unadjusted. Model 2 will adjust for demographic variables (age, race, gender, education level and center). Model 3 will further adjust for other cardiovascular risk factors (adiposity measure, blood pressure, heart rate, smoking status, alcohol habit, physical activity, diabetes, hypertension, dyslipidemia, kidney function and damage and inflammation). Model 4 will additionally account for cardiac echo parameters of LV remodeling and function (LV hypertrophy, concentric remodeling and diastolic dysfunction). We will repeat the analysis after stratifying the study sample by

age, gender, race, and presence/absence of comorbidities such as obesity, hypertension and diabetes. The interaction will be tested by contrasting models with and without interaction terms based on likelihood ratio test. We will also treat cardiac damage and overload variables as dichotomized variables based on clinical cutpoints for elevation (e.g., hs-TnT >14 ng/L and NT-proBNP >400 pg/ml). We will run logistic regression models on dichotomized dependent variables using the same statistical plan outlined for the linear regression analyses. All tests will be considered to be significant at the level of $p < 0.05$.

Limitations:

A cross-sectional design will not allow us to evaluate causality and temporality of the associations. As with any observational study, we will not be able to rule out the possibility of residual confounding. The results may not be generalizable to younger population or ethnic groups other than whites and blacks.

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.csc.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)?

To our knowledge, the following two proposals incorporate both PWVs and echo parameters, but neither of them deal with cardiac biomarkers. Nonetheless, Dr. Susan

Cheng, who is a co-author of both projects and a member of the ARIC PWV Working Group joins this new proposal. Also, we have confirmed no existence of overlapped proposals with the ARIC PWV Working Group.

#2531: Ventricular-arterial coupling in elderly people. The ARIC study

#2550: Utility of Heart-Carotid Pulse Wave Velocity in a Population Based Cohort

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.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.

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 pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes ____ No.

References

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