

**ARIC Manuscript Proposal #2239**

**PC Reviewed:** 10/8/13  
**SC Reviewed:** \_\_\_\_\_

**Status:** A  
**Status:** \_\_\_\_\_

**Priority:** 2  
**Priority:** \_\_\_\_\_

**1.a. Full Title:** Hemodynamic determinants of blood pressure in older adults

**b. Abbreviated Title (Length 26 characters):** BP and hemodynamics

**2. Writing Group:**

Hirofumi Tanaka, Susan Cheng, Scott Solomon, Gerardo Heiss, Natalia Gouskova, others welcome

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

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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 is to begin when the final ARIC dataset from the visit 5 becomes available. We plan to complete the manuscript within one year from release of the data.

**4. Rationale:** Arterial blood pressure increases with advancing age in industrialized countries, resulting in a high prevalence of essential hypertension contributing to age-related increases in risk of a number of cardiovascular disorders<sup>1</sup>. While systolic blood pressure rises continuously, diastolic blood pressure plateaus and tends to decline after

50-60 years of age<sup>2</sup>. As a result, pulse pressure increases markedly with advancing age, resulting in a high prevalence of isolated systolic hypertension<sup>3</sup>.

Although the trend of age-associated increases in blood pressure is well established, it remains unclear what hemodynamic factors determine blood pressure levels in older adults. Arterial blood pressure can be divided into 2 primary components: steady and pulsatile. The steady component of blood pressure or mean arterial pressure is a critically important cardiovascular measure as it is an effective pressure that determines perfusion to the systemic organs. Mean arterial pressure is determined exclusively by cardiac output and total peripheral resistance as governed by the Ohm's law. The hemodynamic factors that influence the pulsatile component are much more complex. Systolic blood pressure is governed by a number of hemodynamic factors, including arterial stiffness, stroke volume, and left ventricular ejection fraction whereas the primary hemodynamic determinants of diastolic pressure include total peripheral resistance, heart rate, arterial stiffness, and systolic blood pressure. The relative contribution of each hemodynamic factor is currently unknown especially in older adults as most of the available evidence is primarily derived from circulatory modeling studies or comparisons with a single hemodynamic variable<sup>4,5</sup>. The ARIC study provides a unique opportunity to evaluate a comprehensive number of hemodynamic determinants of blood pressure in a population-based cohort of older adults. An additional benefit of the ARIC database is that the separate analyses can be performed for both peripheral (i.e., brachial) and central (i.e., carotid) blood pressure.

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

-To describe hemodynamic determinants of systolic, mean, and diastolic blood pressure in older adults.

We hypothesize that pulse wave velocity is the primary determinant of systolic blood pressure.

##### **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:** The cross-sectional study sample will include individuals who participated in the ARIC visit 5.

**Primary dependent variables:** Brachial systolic, mean, diastolic blood pressure, and pulse pressure. Carotid systolic blood pressure and pulse pressure.

**Independent variables:** Hemodynamic determinants of blood pressure (cardiac output and total peripheral resistance for mean arterial pressure; arterial stiffness, stroke volume, and left ventricular ejection fraction for systolic blood pressure; total peripheral resistance, heart rate, augmentation index, arterial stiffness as assessed by pulse wave velocity, and systolic blood pressure for diastolic blood pressure)

**Exclusions:** Missing information on PWV, blood pressure, and antihypertensive medication use; antihypertensive medications; 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 Analyses:**

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.

The relation between arterial blood pressure and hemodynamic determinants will be examined among individual subjects initially using univariate correlation analysis and bivariate plots. Quantile regression will be used to characterize the effect of the hemodynamic determinants at specific percentiles (quantiles) of blood pressure, and forward stepwise multiple regression analyses and partial correlational analyses will be used to examine independent associations between blood pressure variables and hemodynamic variables.

In addition to the primary analyses plan that excludes the majority of the participants, secondary analyses will be performed

- 1) Fit same models, using participants who are on antihypertensive medications (no arrhythmias) - and compare findings with primary analysis;
- 2) Fit same models, using participants who have arrhythmias (no medications) - and compare findings with primary analysis;
- 3) Keep participants on medications and with arrhythmias in the sample, and fit same models but adjusting for medication use, interaction between medication use and other covariates, and possibly also adjusting for having arrhythmias.

**Limitations:**

Some PWV measurements are missing due to technical errors, participant factors and scheduling conflicts. 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  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>  
 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)?

N/A

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.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](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.

## References

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2. Kannel WB, Gordon T. Evaluation of cardiovascular risk in the elderly: The framingham study. *Bull NY Acad Med.* 1978;54:573-591
3. Benetos A, Safar M, Rudnichi A, Smulyan H, Richard JL, Ducimetiere P, Guize L. Pulse pressure: A predictor of long-term cardiovascular mortality in a french male population. *Hypertension.* 1997;30:1410-1415
4. Messerli FH, Frohlich ED, Suarez DH, Reisin E, Dreslinski GR, Dunn FG, Cole FE. Borderline hypertension: Relationship between age, hemodynamics and circulating catecholamines. *Circulation.* 1981;64:760-764
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