

ARIC Manuscript Proposal #2765

PC Reviewed: 6/7/16

Status: A

Priority: 2

SC Reviewed: _____

Status: _____

Priority: _____

1.a. Full Title: Relationship of Blood Pressure Parameters with High Sensitivity Cardiac Troponin-T and N-Terminal Prohormone of Brain Natriuretic Peptide in the Elderly: The Atherosclerosis Risk in Communities Cohort Study

1.b. Abbreviated Title (Length 26 characters):

2. Writing Group: Nidhi Madan, Kunihiro Matsushita, Ron C. Hoogeveen, Christie M. Ballantyne, Elizabeth Selvin, John W. McEvoy, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _NM_ **[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: We aim to submit this manuscript to the ARIC publications committee in <12 months from this date.

4. Rationale:

Aging is commonly associated with significant structural and functional changes in the cardiovascular system. For example, a decrease in distensibility of large arteries, such as the aorta, occurs with age and increases the risk of hypertension (1); an important cardiovascular disease risk factor in the elderly. (2) It is postulated that large arterial vessels stiffen because the elastic tissue in the vessel wall is progressively replaced with collagen over time. In addition to these structural changes, the cardiovascular (CV) system undergoes several other functional changes with aging. (3, 4) Increased pulse wave velocity among older adults results in earlier return of reflected waves from the periphery to the proximal aorta and, consequently, alteration of the arterial wave contour. (5) These reflected blood pressure (BP) waves add to antegrade waves to produce late systolic BP (SBP) augmentation, which is calculated using the augmentation index. (4, 6)

Another functional change with aging is the decline in flow-mediated arterial dilation that occurs secondary to decreased endothelium-derived nitric oxide. (7) Therefore, the vasodilation that normally occurs in response to flow-related SBP increases is compromised. (4) Furthermore, increased central aortic stiffness contrasts with minimal changes in peripheral arterial tone in the elderly. This results in a reversal of the normal central-to-peripheral arterial stiffness gradient, a finding which has been implicated in the development of macro- and micro-vascular diseases in older populations. (8)

The above structural and functional changes tend to result in a gradual rise in the SBP with age, with less impact of diastolic BP (DBP). (3, 9) This phenomenon characterizes a condition known as isolated systolic hypertension (ISH), defined by SBP > 140 and DBP < 90 mmHg. If ISH is left untreated, it can further exacerbate age-related arterial stiffness, forming a vicious cycle. (10) In addition, DBP, which increases up to 50-60 years of age, starts to decline thereafter. This late fall in DBP with continued increase in SBP often results in an increase in pulse pressure among the elderly, even in otherwise normotensive individuals (5). Studies have suggested that elevated pulse pressure may be one of the strongest predictors of cardiovascular risk and mortality in older populations (11), leading some experts to suggest targeting antihypertensive therapy towards lowering pulse pressure in the elderly. (12)

However, antihypertensive therapy has a number of potential complications- such as kidney impairment, orthostasis, and falls- which tend to be more pronounced in the elderly. Therefore, personalized biomarkers of risk are attractive targets to help guide the allocation of antihypertensive drugs among elderly persons with altered BP parameters (such as ISH or elevated pulse pressure). In particular, because elevated SBP (which is present in ISH and typically in persons with elevated pulse pressure) is an important determinant of myocardial stress secondary to increased cardiac afterload and myocardial energy requirements, (13) biomarkers of myocardial damage and stress may be most suitable in guiding the treatment of elderly persons at risk. Novel high sensitivity cardiac troponin T (hs-cTnT) assays indicate subclinical myocardial damage among asymptomatic individuals and hs-cTnT has been demonstrated to be an independent predictor of all-cause mortality, cardiovascular death, heart failure, stroke and sudden cardiac death. (14-18) The association of hs-cTnT with incident hypertension and left ventricular hypertrophy (LVH) in patients with no known cardiovascular disease was shown in a recent study conducted on the Atherosclerosis Risk in Communities (ARIC) population (16). However, the impact of the age-specific changes in blood pressure parameters, described above, on the level of hs-TnT in the blood has, thus far, not been extensively studied.

Brain natriuretic peptide (BNP) is another biomarker that is synthesized by the ventricular myocardium and released into the bloodstream in response to increased left ventricular load or hemodynamic stress. Based on several lines of evidence, circulating levels of BNP or N-terminal prohormone of brain natriuretic peptide (NT-proBNP) have been used in the diagnosis of congestive heart failure, and in the prognostication of patients admitted for decompensated heart failure (19) and acute coronary syndrome. (20) Higher plasma levels of BNP have also been found in patients with hypertension compared to normotensive individuals. (21) N-terminal-proBNP (NT-proBNP) is a stable cleavage product of proBNP and elevated levels have been associated with hypertension in prior cross-sectional studies. (22) A prior ARIC study showed a relationship between NT-proBNP level and the risk of developing hypertension over a maximum follow up period of 14 years in middle-aged adults in the ARIC cohort. (23) However, the impact of age-dependent changes in BP parameters on levels of NT-proBNP (a biomarker of left ventricular strain) is unknown.

Therefore, we aim to examine the cross-sectional relationship between characteristic blood pressure patterns of the elderly (e.g., isolated systolic hypertension, increased pulse pressure, increased augmentation index) and subclinical myocardial damage as measured by hs-TnT. In a related secondary analysis, we will also test for any correlation between these BP patterns and NT-proBNP levels. Our study may have important implications for the cardiovascular risk stratification and prognostication of older adults. Additionally, hs-cTnT and NT-proBNP could prove useful in providing appropriate and timely pharmacological treatment for abnormal BP patterns in older populations and may facilitate the reversal of subclinical myocardial injury in these patients.

5. Main Hypothesis/Study Questions:

Aim 1: To determine the cross-sectional relationship between pulse pressure and high sensitivity cardiac troponin measured at ARIC visit 5 in patients ≥ 65 years of age.

Aim 2: To determine the cross-sectional relationship between isolated systolic hypertension and high sensitivity cardiac troponin measured at ARIC visit 5 in patients ≥ 65 years of age.

Aim 3: To determine the cross-sectional relationship between augmentation index with the level of high sensitivity cardiac troponin measured at ARIC visit 5 in patients ≥ 65 years of age.

Aim 4: To repeat testing of hypotheses one through three using NT-proBNP measured at visit 5 as the outcome variable.

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 observational study

Inclusion criteria:

1. All patients equal to or more than 65 years of age who attended ARIC visit 5 and had measurement of hs-cTnT will be included in the study.

Exclusion criteria:

1. All patients <65 years of age

Variables:

The following variables will be analyzed:

1. Exposure variables:

- A. Systolic blood pressure (SBP), Diastolic blood pressure (DBP)
- B. Mean BP: Defined as $(SBP + 2 * DBP) / 3$

These variables will be used to derive the following:

- a. Isolated Systolic Hypertension (ISH): This is defined as $SBP > 140$ and $DBP < 90$. We will label ISH as a binary categorical exposure
- b. Pulse pressure (PP): Defined as the difference between SBP and DBP. The increase in pulse pressure will be modeled as a categorical exposure by quartile and as a continuous exposure per mm Hg.
- c. Augmentation index (AI): The augmentation index is a numerical value that indicates the percentage of the reflected pressure wave with respect to the driven pressure wave. It is calculated by obtaining the post-systolic component (P2) after subtraction of the maximum wave height of the pre-systolic component (P1), which is expressed as 'delta P'.

$$AI (\%) = (\text{delta P}) / PP \times 100$$

For our study, we will use results from the OMRON Pulse Wave Unit TU-100 connected to the BP-203RPE Series of Non-invasive Vascular Screening Devices to derive the augmentation indices and electrocardiographic measurements. The AI parameter depends on the intensity of the reflected wave, which in turn is determined by the size and elasticity of the smaller arteries and arterioles.

- i. Carotid augmentation index,
 - ii. Mean of L and R Brachial augmentation indices
2. Covariates: Age (years), Gender, race-center, Body height, Body mass index (BMI, in kg/m^2), smoking (current; former; never), alcohol intake (current; former; never), hypertension medication use (yes; no), LVH by electrocardiogram (yes; no), diagnosed diabetes (yes; no; defined as a self-reported physician diagnosis of diabetes or current use of diabetic medications), LDL-cholesterol (mg/dl), HDL-cholesterol (mg/dl), triglycerides (mg/dl), current use of cholesterol lowering medication (yes; no), and estimated glomerular filtration rate in $\text{ml}/\text{min}/1.73\text{m}^2$. In addition, we will also include data on hypertension medications like beta- blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, calcium channel blockers and diuretics.
 3. Outcome variables: Serum level of hs-c-TnT obtained on ARIC visit 5. Secondary analyses will evaluate NT-proBNP level as the outcome variable.

Statistical analyses:

a) Descriptive statistics: Baseline characteristics will be summarized using descriptive statistics, which are, mean (standard deviation) or median (inter-quartile range; IQR) for continuous variables and percentage for categorical or nominal variables. We will divide our study population based on the exposure variables into the following groups:

1. Isolated systolic hypertension (yes or no)
2. Pulse pressure quartiles
3. Augmentation index quartiles

Baseline continuous variables will be compared between above groups using Student's t-test or One-Way Analysis of Variance (ANOVA), as appropriate. Pearson's chi-square test will be used for comparison of categorical/nominal variables.

We will compute crude unadjusted proportions to obtain the proportion of individuals with detectable and elevated hs-TnT among each of the above groups.

b) Regression models:

The primary outcome variable will be the blood level of hs-c-TnT, described categorically as (a) detectable hs-cTnT (<5 or >=5ng/L), and (b) elevated hs-cTnT (<14 or >=14). Age-gender specific cut-offs will also be used. (24) Univariate and multivariate logistic regression models will be used to calculate odds ratios between the above described characteristic BP patterns in the elderly as exposures and the hs-c-TnT category as the outcome. We will also construct linear models to examine the association between these BP patterns and hs-cTnT as a continuous outcome variable. These linear variables will be repeated for NT-proBNP outcome assessment. We will use age, gender, race-center adjusted models for logistic and linear regression. More fully adjusted models will be created to account for height, BMI, diabetes status, creatinine, hypertension medication use, LDL-cholesterol, HDL-cholesterol, triglycerides, statin use. Additional models, adjusting for BP medication use and type (e.g. diuretics yes/no) will also be constructed. Statistical significance will be claimed at a p-value <=0.05. Analyses will be performed with Stata 14 (StataCorp, College Station, Texas).

c) Secondary analyses:

We will stratify the above mentioned groups by hypertension treatment status and perform a secondary analyses to explore the relationship of hypertension treatment status with hs-TnT or NT-proBNP. In addition, we plan to perform a sensitivity analyses excluding patients with prior coronary heart disease and diagnosed heart failure from the analyses.

Limitations:

- As with all observational studies, we will not be able to eliminate the possibility of residual confounding despite rigorous adjustment for known risk factors.

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

MSP #2721. Arterial stiffness and subclinical cardiac damage and overload in older adults: The Atherosclerosis Risk in Communities (ARIC) Study. This proposal plans to study pulse wave velocity, and not the parameters of interest in our study (ISH, pulse pressure, augmentation index).

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)?

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ___ **X ___ Yes ___ ___ No**

11.b. If yes, is the proposal

___ **X** ___ **A. primarily the result of an ancillary study (list number* 2009.16 and 2008.10)**

___ **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.

References

1. O'Rourke MF, Hashimoto J. Mechanical factors in arterial aging: a clinical perspective. *Journal of the American College of Cardiology*. 2007 Jul 3;50(1):1-13. PubMed PMID: 17601538. Epub 2007/07/03. eng.
2. van den Hoogen PC, Feskens EJ, Nagelkerke NJ, Menotti A, Nissinen A, Kromhout D. The relation between blood pressure and mortality due to coronary heart disease among men in different parts of the world. Seven Countries Study Research Group. *The New England journal of medicine*. 2000 Jan 6;342(1):1-8. PubMed PMID: 10620642. Epub 2000/01/06. eng.
3. Pearson JD, Morrell CH, Brant LJ, Landis PK, Fleg JL. Age-associated changes in blood pressure in a longitudinal study of healthy men and women. *The journals of gerontology Series A, Biological sciences and medical sciences*. 1997 May;52(3):M177-83. PubMed PMID: 9158560. Epub 1997/05/01. eng.
4. Aronow WS, Fleg JL, Pepine CJ, Artinian NT, Bakris G, Brown AS, et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. *Journal of the American Society of Hypertension : JASH*. 2011 Jul-Aug;5(4):259-352. PubMed PMID: 21771565. Epub 2011/07/21. eng.
5. McEniery CM, Cockcroft JR. Does arterial stiffness predict atherosclerotic coronary events? *Advances in cardiology*. 2007;44:160-72. PubMed PMID: 17075206. Epub 2006/11/01. eng.
6. Vaitkevicius PV, Fleg JL, Engel JH, O'Connor FC, Wright JG, Lakatta LE, et al. Effects of age and aerobic capacity on arterial stiffness in healthy adults. *Circulation*. 1993 Oct;88(4 Pt 1):1456-62. PubMed PMID: 8403292. Epub 1993/10/01. eng.
7. Celermajer DS, Sorensen KE, Spiegelhalter DJ, Georgakopoulos D, Robinson J, Deanfield JE. Aging is associated with endothelial dysfunction in healthy men years before the age-related decline in women. *Journal of the American College of Cardiology*. 1994 Aug;24(2):471-6. PubMed PMID: 8034885. Epub 1994/08/01. eng.
8. Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, et al. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. *Hypertension*. 2004 Jun;43(6):1239-45. PubMed PMID: 15123572. Epub 2004/05/05. eng.
9. Vasan RS, Beiser A, Seshadri S, Larson MG, Kannel WB, D'Agostino RB, et al. Residual lifetime risk for developing hypertension in middle-aged women and men: The Framingham Heart Study. *Jama*. 2002 Feb 27;287(8):1003-10. PubMed PMID: 11866648. Epub 2002/02/28. eng.
10. Franklin SS, Gustin Wt, Wong ND, Larson MG, Weber MA, Kannel WB, et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation*. 1997 Jul 1;96(1):308-15. PubMed PMID: 9236450. Epub 1997/07/01. eng.
11. Franklin SS, Larson MG, Khan SA, Wong ND, Leip EP, Kannel WB, et al. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. *Circulation*. 2001 Mar 6;103(9):1245-9. PubMed PMID: 11238268. Epub 2001/03/10. eng.

12. Blacher J, Staessen JA, Girerd X, Gasowski J, Thijs L, Liu L, et al. Pulse pressure not mean pressure determines cardiovascular risk in older hypertensive patients. *Arch Intern Med*. 2000 Apr 24;160(8):1085-9. PubMed PMID: 10789600. Epub 2000/05/02. eng.
13. Katz LN, Feinberg H. The relation of cardiac effort to myocardial oxygen consumption and coronary flow. *Circulation research*. 1958 Sep;6(5):656-69. PubMed PMID: 13573596.
14. Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. *Circulation*. 2011 Apr 5;123(13):1367-76. PubMed PMID: 21422391. Pubmed Central PMCID: 3072024. Epub 2011/03/23. eng.
15. de Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA : the journal of the American Medical Association*. 2010 Dec 8;304(22):2503-12. PubMed PMID: 21139111. Epub 2010/12/09. eng.
16. deFilippi CR, de Lemos JA, Christenson RH, Gottdiener JS, Kop WJ, Zhan M, et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. *JAMA : the journal of the American Medical Association*. 2010 Dec 8;304(22):2494-502. PubMed PMID: 21078811. Pubmed Central PMCID: 3559101. Epub 2010/11/17. eng.
17. Hussein AA, Gottdiener JS, Bartz TM, Sotoodehnia N, Defilippi C, Dickfeld T, et al. Cardiomyocyte Injury Assessed by a Highly Sensitive Troponin Assay and Sudden Cardiac Death in the Community: The Cardiovascular Health Study. *Journal of the American College of Cardiology*. 2013 Aug 7. PubMed PMID: 23973690. Epub 2013/08/27. Eng.
18. Eggers KM, Al-Shakarchi J, Berglund L, Lindahl B, Siegbahn A, Wallentin L, et al. High-sensitive cardiac troponin T and its relations to cardiovascular risk factors, morbidity, and mortality in elderly men. *American heart journal*. 2013 Sep;166(3):541-8. PubMed PMID: 24016505. Epub 2013/09/11. eng.
19. Gardner RS, Ozalp F, Murday AJ, Robb SD, McDonagh TA. N-terminal pro-brain natriuretic peptide. A new gold standard in predicting mortality in patients with advanced heart failure. *Eur Heart J*. 2003 Oct;24(19):1735-43. PubMed PMID: 14522568. Epub 2003/10/03. eng.
20. de Lemos JA, Morrow DA, Bentley JH, Omland T, Sabatine MS, McCabe CH, et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *The New England journal of medicine*. 2001 Oct 4;345(14):1014-21. PubMed PMID: 11586953. Epub 2001/10/06. eng.
21. Nishikimi T, Yoshihara F, Morimoto A, Ishikawa K, Ishimitsu T, Saito Y, et al. Relationship between left ventricular geometry and natriuretic peptide levels in essential hypertension. *Hypertension*. 1996 Jul;28(1):22-30. PubMed PMID: 8675258. Epub 1996/07/01. eng.
22. Rivera M, Talens-Visconti R, Salvador A, Bertomeu V, Miro V, Garcia de Burgos F, et al. [NT-proBNP levels and hypertension. Their importance in the diagnosis of heart failure]. *Rev Esp Cardiol*. 2004 May;57(5):396-402. PubMed PMID: 15151773. Epub 2004/05/21. Hipertension y valores de NT-proBNP. Su importancia en el diagnostico de insuficiencia cardiaca. spa.
23. Bower JK, Lazo M, Matsushita K, Rubin J, Hoogeveen RC, Ballantyne CM, et al. N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) and Risk of Hypertension in the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Hypertens*. 2015 Oct;28(10):1262-6. PubMed PMID: 25783741. Pubmed Central PMCID: Pmc4580540. Epub 2015/03/19. eng.
24. Gore MO, Seliger SL, Defilippi CR, Nambi V, Christenson RH, Hashim IA, et al. Age- and sex-dependent upper reference limits for the high-sensitivity cardiac troponin T assay. *Journal of the American College of Cardiology*. 2014 Apr 15;63(14):1441-8. PubMed PMID: 24530665. Pubmed Central PMCID: 3984900. Epub 2014/02/18. eng.