ARIC Manuscript Proposal #2268

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SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Abdominal aorta diameters and arterial stiffness

b. Abbreviated Title (Length 26 characters): Aorta diameters and stiffness


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

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3. Timeline: Work will begin upon approval, and will produce a manuscript within 8 months.

4. Rationale: Arterial stiffness is a known predictor of cardiovascular events, cardiovascular mortality and all-cause mortality [1-7]. Arterial stiffening begins early in life as a progressive pathophysiological process that occurs in large elastic arteries and comprises of structural and cellular transformations. Large elastic arteries (arterial vessels with a diameter reaching 2.5 cm) have a characteristic wall structure made of three layers: tunica intima, tunica media, and tunica adventitia, from the lumen outward. At a cellular level, the tunica intima is made of endothelial
cells lined externally with a layer of elastic fibers. The tunica media constitutes the thickest layer, and its constituents are smooth muscle cells that secrete elastin and collagen proteins. The tunica adventitia is primarily made up of connective tissue that contains collagenous fibers, elastic fibers, fibroblasts and macrophages. The ratio of elastin to collagen varies along the arterial tree. Large elastic arteries more proximal to the heart contain more elastin compared to collagen, while more distal to the heart the ratio is reversed. A threshold point in this respect is found near the diaphragm where the abdominal aorta begins[8].

The compliance of large elastic arteries is primarily maintained by secretion and degradation of elastin and collagen proteins[9]. Arterial stiffness develops due to disequilibrium in this process and compositional changes in the arterial wall resulting in diminished amounts of normal elastin coupled with increased amounts of abnormal collagen[9, 10]. For reasons not fully established the abdominal aorta is a site of predilection and of early onset of atherosclerosis. Furthermore, differences in the degree of arterial stiffening occur in various segments of the aorta, due to inherent variability in the elasticity of the anatomical aortic segments[11]. Insights into this process are of particular interest at the abdominal aorta in the setting of dilatation and the consequent development of abdominal aortic aneurysms (AAA).

As mentioned, arterial stiffness progresses with aging, and the degree of stiffening carries predictive value for cardiovascular mortality and morbidity, even in apparently healthy individuals [12]. The process of arterial stiffening can be accelerated by cardiovascular risk factors, including arterial hypertension[13-16], tobacco use [17-19], elevated plasma glucose level [20-22], and elevated lipid levels [23, 24]. Risk factors common to arterial stiffness and AAA include aging, tobacco use, and arterial hypertension [13, 14, 16, 25].

The literature examining the association between abdominal aorta diameter (AAD) and arterial stiffness is quite limited. As predicted by the inverse relation between pulse wave velocity (PWV) and the square root of the abdominal aortic diameter [14], arterial stiffness measured by carotid femoral pulse wave velocity (cfPWV) was reported to be lower in individuals with abdominal aortic aneurysm prior to endovascular aneurysm repair[26, 27], cfPWV also was reported to be higher in individuals with AAA compared to individuals without AAA[28]. The relationship between arterial stiffness and AAD has not been characterized in a community-based population of older adults, and to our knowledge the cross-sectional association between the abdominal aorta diameters and arterial stiffness has not been examined.

Although arterial stiffness can be assessed using various techniques and equations (Appendix 1) [29], pulse wave velocity has been used more frequently in recent studies, and is referred to as the “gold-standard” measurement of arterial stiffness [30]. Arterial stiffness measured by pulse wave velocity is dependent on the arterial material wall properties, and the wall thickness/lumen diameter ratio. This is best described by Moens–Korteweg equation \( \text{PWV} = \sqrt{\frac{h}{D \rho}} \) [31]. Furthermore, the degree of arterial stiffness measured by pulse wave velocity is currently used in clinical practice in some Asian and European countries to evaluate cardiovascular health and assess cardiovascular morbidity and mortality.
The purpose of the analyses proposed here is to examine the ability of cfPWV to predict the diameter of the abdominal aorta at three pre-specified sites, and to assess whether the degree of arterial stiffness measured by cfPWV is indicative of atherosclerotic changes in the abdominal aorta. We acknowledge the dependence between pulse wave velocity and abdominal aorta, however this will be addressed in the process of statistical analysis. Further, we propose to examine the association between cfPWV and the shape of the abdominal aorta as defined by analyzing the ultrasonographic imaging taken at proximal, mid, and distal points.

Our conclusions may speak to the potential merit of using the arterial stiffness measures such as cfPWV, as a convenient and reliable non-invasive tool to infer the presence of atherosclerotic changes and dilatation of the abdominal aorta.

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

Our goal is to characterize the relation between central and peripheral arterial stiffness measured by carotid femoral pulse wave velocity (cfPWV), brachial ankle pulse wave velocity (baPWV) and femoral ankle pulse wave velocity (faPWV) respectively, and diameters of the abdominal aorta at a proximal, mid-aorta and distal locations in a population based, bi-ethnic cohort of men and women ages 70-89 years.

**Aims**

I. Describe the distribution of central and peripheral arterial stiffness measured by cfPWV, baPWV, and faPWV respectively, and anterior posterior abdominal aorta diameters at proximal, mid, and distal locations at the cohort Visit 5 examination. Descriptive analyses by age, gender and race will be limited to a characterization of the study population included in these analyses.

- Examine the distribution of central and peripheral arterial stiffness by age, gender, and race.
  - We hypothesize that stratifying by age; gender and race will elicit differences in the distribution of central and peripheral arterial stiffness.
- Examine the distribution of abdominal aorta diameters at proximal, mid, and distal locations according to age, gender, and race
  - We hypothesize that stratifying by age, race and gender will elicit differences in the distribution of abdominal aorta diameters at proximal, mid, and distal locations.

II. Characterize the associations between both central, and peripheral arterial stiffness (measured by cfPWV, and faPWV), and abdominal aorta diameters at proximal, mid, and distal locations at the cohort Visit 5 examination.

- Characterize the strength and shape of the association between: central arterial stiffness measured by cfPWV, and abdominal aorta diameters at proximal, mid, and distal locations; and peripheral arterial stiffness measured by faPWV, and abdominal aorta diameters at the three locations stated above.
We hypothesize that increasing levels of cfPWV, and faPWV will be associated with wider abdominal aorta diameters.

We hypothesize that the strength of association will increase from proximal to distal levels of the abdominal aorta.

- Examine the role of demographic characteristics, and history of cigarette smoking, hypertension and type 2 diabetes as covariates and potential effect modifiers of observed associations between cfPWV, and abdominal aorta diameters and shape; and between faPWV, and abdominal aorta diameters and shape.
  - We hypothesize that strength of association between arterial stiffness and abdominal aorta diameters will vary due to potential effect modifiers such as cigarette smoking, hypertension and type 2 diabetes.

III. Examine the differences in the associations between central, and peripheral arterial stiffness (measured by cfPWV, and faPWV respectively), and both the anterior-posterior (AP), and transverse abdominal aorta diameters.

- We hypothesize the strength and type of association will vary by the abdominal aorta diameter plane examined.

- Examine the differences in the associations between peripheral arterial stiffness measured by faPWV and the anterior-posterior (AP), and transverse abdominal aorta diameters.
  - We hypothesize the strength and type of association will vary by the abdominal aorta diameter plane examined.

- Examine the role of demographic characteristics, and history of cigarette smoking, hypertension and type 2 diabetes as covariates and potential effect modifiers of observed associations between faPWV and abdominal aorta diameters and shape.

IV. Characterize the level of peripheral arterial stiffness measured by faPWV, and the deviations in the shape of abdominal aorta evaluated by ultrasound of the abdominal aorta at three levels.

- We hypothesize that higher levels of faPWV will be associated with abnormally shaped abdominal aorta.

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 analysis of participants at ARIC visit 5, with inclusion of historical information on covariates/effect modifiers.

**Independent Variables**
Central arterial stiffness measured by cfPWV, peripheral arterial stiffness measured by faPWV, and baPWV are measured with the Omron VP-1000 plus system (Colin Co., Ltd., Komaki, Japan). The device measures cfPWV, baPWV, and faPWV. The distance from the location of the carotid artery recording site to the femoral artery recording site is measured using a Rosscraft Anthropometric Segmometer (Surrey, Canada). The distance traveled in centimeters (cm) is calculated using the formula: distance traveled (cm) = carotid-femoral distance (cm) – (supra-sternal notch – carotid distance (cm)).

Dependent Variable(s)
Abdominal aorta diameters (AAD) measured by high resolution, real time duplex ultrasound (Philips IE33). This examination was performed by trained and certified sonographers. Transverse images at three different segments of the abdominal aorta were taken to identify the anterior-posterior and transverse diameters.

Covariates
Covariates of interest include; gender, age, smoking status, systolic blood pressure, diabetes mellitus, diastolic blood pressure, blood pressure-lowering treatments, body surface area measure by body mass index (BMI), and it is measured by the division of weight in kilograms by the squared height in meters (kg/m²).

Eligible Observations/Sample
All participants with pulse wave velocity values and abdominal aorta diameter values obtained at visit five will be included. An ultrasound examination of the aorta was not performed on participants with a history of previous abdominal aortic aneurysm repair or previous aortic bypass surgery for occlusive atherosclerotic disease. Since the excluded participants may have higher pulse wave velocity readings compared to their counterparts with AAA that did not have corrective surgical procedures, informative censoring is present and sensitivity analysis will address the potential bias introduced.

Analyses
The AA diameters as well as arterial stiffness measured by cfPWV, baPWV, and faPWV are processed and will be analyzed on a continuous scale, and as a clinically defined binary dependent variable (large vs. not large diameter). In addition, the overall shape of the abdominal aorta will be evaluated by calculating the change from the average diameter from existing literature at each level (proximal, mid, and distal) and the value as measured by the abdominal aorta ultrasound in visit 5.

Aortic diameter measurements will be retrieved from the over-read of the AAO files by radiologists (giving precedence to the last reading for a participant in that file), and from the data capture AAT files for those not over-read by radiology.

Covariates will be included in the analyses if known or suspected to be biologically plausible risk factors for arterial stiffness, and could potentially confound the relationship between AAD and arterial stiffness. These factors include gender, age, smoking status, diabetes, systolic blood pressure, diastolic blood pressure, blood pressure-lowering treatments, and BMI (kg/m²).

Bivariant comparisons of each independent variable to the abdominal aorta diameters will be explored and summary statistics will be estimated. The relationship between cfPWV, faPWV and
the dependent variable will be examined modeling ADD as a binary and continuous variable. In its continuous form we expect an inverse monotonic relationship between cfPWV and AAD, and between faPWV and AAD. To avoid making assumptions about linearity the form of this relationship will be characterized in the course of model fitting.

Attrition/Informative loss to follow-up
Attrition and selective loss to follow-up over the prolonged cohort follow-up period will be quantified, and the degree to which it is selective according to the exposures considered here will be examined. If warranted, inverse weighing according to probability of attrition will be applied according to the degree of selective loss to follow-up.

Limitations
The ARIC Visit 5 examinees represent a selected subset of this closed cohort. Achieving internal validity/unbiased estimates despite selective loss of follow-up will be our target. African American participants exhibited considerable attrition. Caution will be exercised in generalizing the results to other populations of older adults, and extra caution will be warranted in making conclusions for differences attributed to race. Ultrasound scans of the abdominal aorta were not performed on participants with a history of abdominal aortic aneurysm repair or previous aortic bypass surgery for occlusive atherosclerotic disease, thus introducing informative censoring. Sensitivity analyses will be used to estimate the magnitude of this concern and its potential impact.

7.a. Will the data be used for non-CVD analysis in this manuscript?  _____ Yes  __×__ 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

  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)?

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* AS 2009.18: “Identifying Genetic and Epidemiological Risk Factors for Abdominal Aortic Aneurysm”, R01HL103695 )  

   ___ 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.nc.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.nc.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:


### Table 2  Indices of arterial stiffness

<table>
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<th>Index</th>
<th>Definition</th>
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<th>Comments</th>
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<tr>
<td>Incremental Elastic Modulus</td>
<td>It is the “local” slope of the incremental change in circumferential stress and the incremental change in circumferential length of the wall material at the operating range of stress and strain.</td>
<td>( \frac{3 \times (1-\nu^2/WCSA)}{DC} ) where WCSA equals: ((D_i^2 + D_e^2) \times \frac{\pi}{4} )</td>
<td>Indicator of the stiffness of the arterial wall material. Also called Young’s incremental elastic modulus.</td>
</tr>
<tr>
<td>Compliance</td>
<td>Change in arterial volume relative to the change in arterial pressure</td>
<td>( \frac{\Delta V}{\Delta P} )</td>
<td>Influenced by wall stiffness, arterial size and wall thickness.</td>
</tr>
<tr>
<td>Elastance</td>
<td>Change in arterial pressure relative to the change in arterial volume, or the inverse of compliance</td>
<td>( \frac{\Delta P}{\Delta V} )</td>
<td>Influenced by wall stiffness, arterial size and wall thickness.</td>
</tr>
<tr>
<td>Distensibility</td>
<td>Fractional change in arterial volume relative to the change in arterial pressure</td>
<td>( \frac{\Delta V}{\Delta P} )</td>
<td>Influenced by wall stiffness and thickness. It is analogous to compliance, but normalized for arterial size.</td>
</tr>
<tr>
<td>Compliance Coefficient</td>
<td>Absolute change in cross-sectional area relative to the change in arterial pressure</td>
<td>( \frac{\Delta A}{\Delta P} )</td>
<td>Estimation of compliance based on cross-sectional (rather than volume) measurements. It relates linearly to compliance under the assumption of a perfectly homogeneous arterial segment and no changes in segmental arterial length.</td>
</tr>
<tr>
<td>Distensibility Coefficient</td>
<td>Fractional change in cross-sectional area relative to the change in arterial pressure</td>
<td>( \frac{\Delta A}{\Delta P} )</td>
<td>Analogous to compliance coefficient, normalized for arterial caliber. It is identical to distensibility under the assumption of a perfectly homogeneous arterial segment and no changes in segmental arterial length. It is inversely proportional to the wall thickness/diameter ratio and the incremental elastic modulus of the wall material.</td>
</tr>
<tr>
<td>Peterson’s Elastic modules</td>
<td>Arterial pressure change for a given fractional diameter change. Also called pressure-strain modulus. Since the ( D \Delta D ) becomes the unit if diameter is doubled, it is often defined as the “Pressure change required for a theoretical 100% increase in diameter”</td>
<td>( \frac{\Delta P}{D} )</td>
<td>Not a measure of the elastic properties of the wall material. Somewhat analogous to the inverse of distensibility, it is influenced by the incremental elastic modulus of the wall material and wall thickness.</td>
</tr>
<tr>
<td>( \beta ) Stiffness Index</td>
<td>Logarithm of the ratio of maximum/minimum pressure over fractional diameter change</td>
<td>( \ln \left( \frac{P_{\text{max}}}{P_{\text{min}}} \right) )</td>
<td>Due to the mathematical correction of the logarithm of ( P_{\text{max}}/P_{\text{min}} ), values within individuals are less sensitive to distending pressure.</td>
</tr>
</tbody>
</table>

WCSA wall cross-sectional area, \( D_e \) external vessel diameter (inter-adventitial diameter) measured in diastole, \( D_i \) internal vessel diameter (interstitial diameter) measured in diastole

\( \Delta P \) is the difference between maximum and minimum pressure. \( \Delta V \) is the difference between the corresponding maximum and minimum volume. 
\( \Delta A \) is the difference between maximum and minimum cross-sectional vessel area. \( D_{\text{max}} \) is the maximum vessel diameter. \( D_{\text{min}} \) is the minimum vessel diameter.