ARIC Manuscript Proposal #2237

PC Reviewed: 10/8/13  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Carotid artery distensibility and pulsatile arterial stiffness in ARIC

b. Abbreviated Title (Length 26 characters): AD and PWV

2. Writing Group:
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Richey Sharrett, Hirofumi Tanaka, others welcome

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

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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 Visit 5 dataset becomes available. We
plan to complete the manuscript within one year from release of the data.
4. **Rationale:**

Aging and exposure to vascular risk factors cause structural changes in the artery such as degeneration of elastin, increases in collagen, and thickening of the arterial wall that leads to arterial stiffness and a widened pulse pressure. Pulsatile measures of central arterial stiffness such as carotid-femoral pulse wave velocity (cfPWV) and carotid artery stiffness are associated with cardiovascular disease and mortality (Blacher, 1998, Blacher, 1999; Meaume, 2001, Vlachopoulos, 2010). Stage I examination of ARIC’s Visit 5 includes measurement of cfPWV, an indirect but established measure of aortic stiffness, and brachial-ankle PWV (baPWV), a measure of central and peripheral arterial stiffness (Tanaka, 2009) that is easier to measure than cfPWV. Measures of carotid artery distensibility were obtained during the ARIC baseline examination and the first cohort re-examination (ARIC Visit 2).

Both cfPWV and carotid artery distensibility are accepted measures of the stiffness of large elastic arteries. PWV is proportional to the square root of vessel stiffness, as shown by the Bramwell-Hill model $PWV = (\rho \times \text{Distensibility})^{1/2}$ with distensibility estimated from the relative change in the lumen area over the local pulse pressure $=\Delta \text{Area}/(\text{Area}_{\text{min}} \times \Delta \text{Pulse Pressure})$, and $\rho$ as blood density (Bramwell, 1922). The Bramwell-Hill model has been validated with aortic PWV and distensibility measured by cardiovascular magnetic resonance, and cfPWV measured by applanation tonometry (Dogui, 2011; Westenberg, 2012). Both studies showed acceptable correlations between these measures that support our use of the Bramwell-Hill model to calculate local PWV from the ARIC carotid distensibility data.

The purpose of the proposed analyses is to examine the degree to which these regional and local measures of stiffness measures rank ARIC participants comparably in middle age and older adulthood. The results may inform the cross-sectional analyses of arterial stiffness at Visit 5, as well as the examination of long-term predictors of arterial stiffness in older adults.

5. **Main Study Questions**

Examine the degree to which carotid artery distensibility measured at ARIC Visit 2, PWV derived at Visit 2 (PWV_der), and cfPWV and baPWV measured at ARIC Visit 5 rank ARIC participants comparably.

We posit that quantile distributions of arterial distensibility (AD), arterial compliance (AC), Peterson’s elastic modulus ($E_p$), Young’s elastic modulus (YEM), stiffness index (SI), and PWV_der will be better aligned with cfPWV than with baPWV.

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:** All individuals who participated in the ARIC visits 2 and 5.

**Exclusions:** Missing information on AD, PWV and exclusions recommended by the ARIC ABI/PWV Working group: participants with BMI>=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 (codes to be specified – temporarily use MSR
Variables of interest:

Pulse Wave Velocity: cfPWV and baPWV are collected as part of the Stage I examination of ARIC’s Visit 5, using the Omron VP-1000 device. The cfPWV and the right baPWV were measured twice each, and the results were averaged. Distance for cfPWV was measured with a segmometer (Rosscraft, Surrey, Canada), and calculated as the suprasternal notch to carotid - carotid to femoral distance. Distance for baPWV was calculated using height-based formulas.

Pulse wave velocity was estimated from the distance between two arterial recording sites divided by transit time. Transit time is defined as the time delay between the proximal and distal ‘foot’ waveforms, i.e., the commencement of the sharp systolic upstroke. The time delays between right brachial and tibial arteries (Tba), between carotid and femoral arteries (Tcf), and between femoral and tibial arteries (Tfa) were obtained. The path length from the carotid to the femoral artery (Dcf) was assessed in duplicate over the surface of the body with a non-elastic tape measure. For patients whose distance between the carotid and femoral artery was not available, Dcf was estimated. The path lengths from the suprasternal notch to brachial artery (Dhb), from suprasternal notch to femur (Dhf), and from femur and ankle (Dfa) were calculated by the machine using the following equations [ARIC protocol]:

\[
\begin{align*}
D_{hb} &= (0.220 \times \text{height (cm)} - 2.07) \\
D_{hf} &= (0.564 \times \text{height (cm)} - 18.4) \\
D_{fa} &= (0.249 \times \text{height (cm)} + 30.7)
\end{align*}
\]

Pulse wave velocity was calculated as follows:

- Carotid-femoral PWV = Dcf / Tcf
- Brachial-ankle PWV = (Dhf + Dfa - Dhb) / Tba

Abdominal aortic strain: Abdominal strain measurements were obtained in a subset of ARIC participants (n= 500 to 800) at visit 5. Abdominal aortic ultrasound images were used to obtain measures of aortic function that include longitudinal and transverse aortic strain, aortic distensibility (distensibility coefficient), and abdominal aortic stiffness (β index).

Carotid Artery Distensibility: During the ARIC cohort Visit 2 examination, b-mode ultrasound was used to collect the common carotid arterial diameter on the left common carotid artery, after the participants had rested in a supine position for at least 20 minutes. The digitized data were processed at the ARIC Ultrasound Reading Center, where the arterial diameter was estimated as the average over an average of 5.5 cycles and the diastolic arterial diameter (DAD) and the arterial diameter change (ADC) between systole and diastole during cardiac cycles were recorded. Concurrent brachial blood pressure was measured every 5 minutes with an automated oscillometric device (1846SX Dinamap); the mean of 2 BP measures before the completion of ultrasound examination was used in calculating arterial stiffness indices.
Traditional indices of arterial stiffness (stress-strain ratio) [Riley, 1992a; Riley, 1992b; Liao, 1999] were estimated as follows:

i. **Arterial distensibility** (AD) is defined as the percent volume increase occurring within an arterial segment during the cardiac cycle divided by the arterial pulse pressure. For the simple model of an artery consisting of a thin walled cylindrical tube, having systolic and diastolic diameters equal to DS and DD, respectively, systolic and diastolic blood pressures equal to SBP and DBP respectively, and pulse pressure (PP) equal to SBP-DBP, arterial distensibility is defined as:

\[
AD\ (\%/kPa) = 100 \times \frac{DS^2 - DD^2}{(PP \times DD^2)}
\]

Arterial distensibility defined in this way is independent of the length of the arterial segment. The unit of measurement is %/kPa where 1 kPa = 7.6 mmHg.

ii. **Arterial compliance** (AC) is defined as the absolute volume increase occurring within an arterial segment during the cardiac cycle divided by the arterial pulse pressure. The artery is assumed to lengthen minimally during the cardiac cycle. Arterial compliance per unit length (1 mm) for a simple model is defined as:

\[
AC\ (\text{mm}^3/kPa) = \pi \times \frac{DS^2 - DD^2}{4 \times PP}
\]

iii. **The pressure-strain elastic moduli** are defined as the arterial pulse pressure divided by the carotid arterial strain (CAS) imposed on the artery during the cardiac cycle. CAS (%) is calculated as \((DS - DD)/DD\).

Peterson’s elastic modulus: \(E_p\) (kPa) = \(PP / CAS\)

Young’s elastic modulus: \(YEM\) (kPa) = \((0.5 \times DD / \text{CIMT}) \times E_p\)

iv. **The stiffness index** was found to be less dependent on arterial blood pressure within individuals (Hirai et al. Circulation 1989; 80:78-86) is defined as the natural logarithm of the ratio of systolic blood pressure to diastolic blood pressure divided by the CAS.

Beta stiffness index: \(SI = \ln (SBP / DBP) / CAS\)

v. **Deriving an estimate of local PWV (PWV_der) from Visit 2 carotid distensibility**

An estimate of PWV will be calculated using the Bramwell-Hill model \(PWV = (\rho \times \text{Distensibility})^{1/2}\) with \(\rho\) as blood density (1,059 kg.m\(^{-3}\)).

\[
PWV\_der = (1,059 \times ((DS^2 - DD^2) / (PP \times DD^2)))^{-1/2}
\]
Statistical Analyses:

We will calculate marginal means and difference in means for cfPWV, baPWV, AD, AC, Ep, YEM, SI and PWV_der by age group, gender and race adjusted for systolic blood pressure (SBP) and heart rate. We will graphically examine and overlay quantiles of cfPWV, baPWV, AD, AC, Ep, YEM, and PWV_der by age group, gender, and race. Quantile regression will be used to evaluate the relationship between distensibility measures and derived PWV at visit 2 with PWV quantiles (see example figure below). Separate models will be constructed for gender and race, adjusted for age, SBP and heart rate. We will replicate the statistical analysis using aortic function parameters among participants who had abdominal aortic ultrasound at visit 5.

![Quantiles for PWV at Visit 5 with distensibility at Visit 2](image)

Attrition

Mortality or loss to follow-up since ARIC visit 2 could plausibly be associated with carotid artery distensibility or stiffness, leading to potential for informative censoring/selection bias. Loss to follow-up, all-cause mortality, and mortality due to cardiovascular causes will be examined according to baseline characteristics at Visit 2, including carotid distensibility and derived stiffness indices. If warranted we will use inverse probability of attrition weighting to account for missing data in quantile regression.
The repeatability of the carotid artery AD measures in ARIC have been reported (Arnett, 1999); similarly, the repeatability and validity of the cfPWV measured by the OMRON VP-1000 have been reported (Cortez-Cooper et al. Am J Cardiol. 2003).

Limitations:

Although the common carotid artery is an elastic artery, its properties only indirectly relate to those of the thoracic aorta, and the carotid AD measures lack a pulsatile component. Another limitation to consider is that blood pressure was obtained at the brachial artery.

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  ____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.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)?

#003 Arterial wall thickness and distensibility (Riley)

#003A The relationship between CVD risk factors and carotid artery distensibility in middle-aged adults (Burke G)

#510 Multiple metabolic syndrome (disorder) and arterial stiffness (Liao D)

#2048 Association of Myocardial Deformational Measures and Arterial Stiffness in the Community (Cheng S)
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.cscd.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.cscd.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


