ARIC Manuscript Proposal #2299

PC Reviewed: 2/11/12  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Clinical and Echocardiographic Correlates of Aortic Strain in the Community

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

2. Writing Group:
   Writing group members: Cristina Quarta, Amil Shah, Hicham Skali, Weihong Tang, Emil Missov, Scott Solomon, Susan Cheng, OTHERS WELCOME

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal: CCQ [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: 2 months. Anticipate two manuscripts will be completed within 6 months after completion of the analyses: one methodology paper, and one reporting the main results.

4. Rationale:
Vascular dysfunction is a key determinant of overall CV morbidity and mortality (1-3). The hallmark of vascular aging is arterial stiffening, which is frequently coupled with abnormal myocardial function (4-6). Increased aortic stiffness reflects the aging structural and functional changes within the vessel wall. As aortic stiffness is frequently coupled with abnormal cardiac function, it is associated with cardiovascular morbidity and is an important independent predictor of future cardiovascular events and all-cause mortality (1-3). The pulse wave velocity (PWV), the distensibility coefficient (DC), the stiffness index β (β) or other M-mode indices have been widely used to non-invasively assess arterial stiffness (7-13). However, these methods provide an indirect assessment of arterial function and are subject to limitations: PWV is known to underestimate early effects of aging on the arterial system and to overestimate stiffness in hypertensive patients (7-10); DC is more sensitive to detect arterial dysfunction early in life, but is less informative in older age (7,9,10,13), and β does not take into account the expansion of the media-intima wall.

Two-dimensional (2D) speckle tracking (ST) imaging is a recent technique which uses standard B-mode images for speckle tracking analysis, in which the speckled pattern is followed frame by frame. Since this speckle pattern is unique for each tissue region, a change between speckles represents the tissue deformation. ST follows these changes and extracts the displacement, velocity, strain and strain rate of a defined tissue segment, allowing the quantification of potentially any biological tissue deformation. 2D ST echocardiography has been shown to provide an angle-independent, well-validated method for assessing the different mechanical properties of cardiac function. Emerging evidence suggest that 2D-ST can offer a simple, direct and accurate determination of large artery stiffness. Small clinical studies suggest that the aortic wall strain can differentiate the presence vs. absence of atherosclerotic plaque, and to detect age-related arterial dysfunction even prior to any detectable changes in PWV or DC (7,11,14-16). In particular, abnormalities in abdominal aortic structure and function may represent a more global marker of vascular risk (14-16), as well as a measure of the arterial dysfunction that can occur in the setting of abnormal ventricular-vascular coupling.

The Atherosclerosis Risk in Communities (ARIC) study began in 1987 and enrolled 15972 individuals aged 45-64 years in four heterogeneous communities in the U.S. (30% African-Americans). Participants have been followed over time with clinical and instrumental assessments. From 2011 to 2013, surviving cohort participants have undergone an updated full clinical and instrumental assessment, which included an echocardiographic evaluation and aortic ultrasonography (non-moving images) at three levels ( supra-renal, mid and infra-renal) of the abdominal aorta. Based on approved ARIC ancillary proposal #2012.16, from September 2012 to May 2013, moving images of the distal (infra-renal) abdominal aorta were also acquired.

5. Main Hypothesis/Study Questions:

Our study hypotheses are as follows:

1. We hypothesize that offline measures of aortic wall strain demonstrate inter- and intra-reader reproducibility that is comparable to the reproducibility of standard image-based measures of vascular function (e.g. DC, β stiffness index).
2. We hypothesize that decreased aortic wall strain is associated with increased burden of cardiovascular risk, as represented by traditional cardiovascular risk factors.

3. We hypothesize that decreased aortic wall strain is also associated with echocardiographic measures of abnormal cardiac structure and function, reflecting abnormal ventricular-vascular coupling, even after adjustment for traditional cardiovascular risk factors.

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 sample.** The study will include all participants who attended Visit 5, underwent cine aortic ultrasonography, and had cine images of adequate quality for strain analyses.

**Conventional image-based assessment of aortic function.** Measurements for calculating the *distensibility coefficient* and *β stiffness index* will be performed using an off-line image analysis system (2D Cardiac Performance Analysis [CPA] v1.1, TomTec Imaging Systems, Untersleissheim, Germany). The *distensibility coefficient (DC)* of the aorta will be calculated as follows: \( D = \Delta A / (Ao \times \Delta P) \), where \( \Delta A \) is the difference in cross-sectional area (CSA) between diastole and systole, \( Ao \) is CSA in diastole, and \( \Delta P \) is the difference between systolic and diastolic pressures. The *β stiffness index* will be calculated as \( \beta = (\ln [Ps/Pd]) \times (Do / \Delta D) \), where \( Ps \) is systolic pressure, \( Pd \) is diastolic pressure, \( Do \) is diastolic diameter, and \( \Delta D \) is the difference in diameter between diastole and systole (ref). Aortic CSA and Do will be measured at the distal level of the abdominal aorta.

**Advanced image-based assessment of aortic function.** Analyses of the aortic strain (*peak circumferential and radial strain*) will be performed using TomTec 2D CPA, which uses a 2D speckle tracking algorithm and allows extracting tissue motion estimates by tracking a user-defined trace drawn along a tissue border. 2D CPA has been validated for the speckle-tracking analysis of LV function. The software for the vascular analysis is similar to that of cardiac short-axis analysis and divides the aortic transverse wall into 6 segments for analysis. Strain analysis will be performed by manually tracing the aortic wall from the transverse image at the distal (infra-renal) level of the aorta (image quality tends to be more optimal at the distal rather than the mid or proximal levels of the abdominal aorta). The peak strain (circumferential and radial) will be calculated as the average value of the 6 segments.

**Statistical Analyses**

1) **Reproducibility.** We will randomly select up to 50 studies of at least adequate or good image quality to evaluate intra-reader and inter-reader reproducibility of aortic strain measurements performed blinded to participant demographic and clinical
information. We will also evaluate intra-reader and inter-reader reproducibility of DC and the β stiffness index. Reproducibility of measures will be assessed using Bland-Altman plots, coefficients of variation, and intra-class correlation coefficients.

2) **Clinical Correlates.** We will use multivariable linear regression to assess the cross-sectional association of aortic strain with demographic characteristics (age, sex, race) as well as traditional cardiovascular risk factors (including body mass index, blood pressure indices, diabetes, hyperlipidemia, and smoking). We will perform these analyses in participants with and without prevalent cardiovascular disease (coronary heart disease, prior stroke/TIA, or heart failure). In secondary analyses, we will assess the association of aortic strain with non-traditional cardiovascular risk factors assessed at visits leading up to and including visit 5, including alcohol use, creatinine, hemoglobin, red cell distribution, brain natriuretic peptide, and high sensitivity troponin T. We will consider analyses in participants with and without presence of plaque visualized on analyzed aortic images. In secondary analyses, we will also use multiplicative interaction terms to test for effect modification by age, sex, and race.

3) **Echocardiographic Correlates.** We will use multivariable linear regression to assess the cross-sectional association of aortic strain with conventional echocardiographic measures of cardiac structure (including LV mass, wall thickness, geometry) and function (including LV ejection fraction, E’) as well as advanced measures of cardiac function (including LV longitudinal strain and circumferential strain). Multivariable models will be performed separately for each echocardiographic measure and will adjust for significant clinical covariates identified in step 2 above, as well as prevalent cardiovascular disease. In secondary analyses, we will use multiplicative interaction terms to test for effect modification by age, sex, and race.

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   X 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 list 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* 2012.16) 

___  B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _______ ________ ________)

Ancillary study #2012.16

*ancillary studies are listed by number at http://www.cscc.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.cscc.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
