1.a. Full Title:

Association of Myocardial Deformational Measures and Arterial Stiffness in the Community

b. Abbreviated Title (Length 26 characters):

Myocardial Deformation and Arterial Stiffness

2. Writing Group:

Writing group members:

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WELCOME

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

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3. **Timeline:** Analyses to begin Winter 2012. A manuscript draft is expected during Spring 2013 / Summer 2013.

4. **Rationale:**

It is now recognized that novel measures of subclinical left ventricular (LV) dysfunction, which may predispose to the eventual development of overt heart failure (HF), can exist even among those without abnormalities in conventional measures of LV structure and function (e.g., LV mass and LV ejection fraction [EF]). Such novel measures of subclinical LV dysfunction, including myocardial strain based measures, may capture among the earliest changes in LV performance that can occur in the progression to HF. The factors that contribute to variation in these novel LV measures are not entirely clear. Although hypertension is likely to play a major role, it has been suggested that conduit arterial stiffness may also be a primary contributor to early subclinical myocardial dysfunction, even after accounting for variation in blood pressure. In a subset of 1100 participants in the Multi-Ethnic Study of Atherosclerosis, we and others observed that carotid arterial stiffness was related to decrements in circumferential LV myocardial strain (assessed using cardiac magnetic resonance) even after adjusting for clinical covariates including blood pressure and anti-hypertensive treatment. More recent studies examining the relation of aortic stiffness with both longitudinal and circumferential LV strain suggest that longitudinal and circumferential strains may be differentially related to arterial stiffness, and in patterns that may be modified by age and sex. However, these studies have been limited to selected samples of less than 100 study participants each. Furthermore, no prior studies have assessed for possible effect modification by race/ethnicity on the relationship between arterial stiffness and myocardial deformation. The echocardiographic data collected at the Atherosclerosis Risk in Communities (ARIC) Study Visit 5 examination presents the unique opportunity to comprehensively investigate LV myocardial deformation in association with tonometric measures of arterial stiffness in a large, bi-racial community-based cohort. Thus, we propose to use speckle-tracking based measures of LV strain to better characterize the myocardial functional abnormalities that are associated with arterial stiffness – and to identify the factors that may promote this association, including clinical characteristics (e.g. age, sex, race, hypertension status) and echocardiographic characteristics (e.g. LV mass, LVEF, and E’).

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

Our main hypothesis is that alterations in longitudinal versus circumferential LV function, assessed via echocardiography, are related to increased arterial stiffness in the community – and that these associations are modified by the presence of select clinical and echocardiographic factors. Specifically, we hypothesize that increased arterial stiffness is associated with reduced longitudinal myocardial deformation overall. We also hypothesize that increased arterial stiffness is associated with a compensatory increase in circumferential myocardial deformation in persons with lower compared to higher cardiovascular risk factor burden, and in individuals with echocardiographic features of concentric as opposed to eccentric LV remodeling. Accordingly, we hypothesize that increased arterial stiffness is associated with a decrease in circumferential
myocardial deformation in persons with higher cardiovascular risk factor burden and in those with echocardiographic features of eccentric LV hypertrophy.

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).

The study sample will include individuals who attended the ARIC Visit 5 examination and who underwent both echocardiography and arterial tonometry at this visit.

Dependent variables. The primary dependent variables of interest will include the following echocardiographic measures of LV function: global longitudinal strain (GLS), global circumferential strain (GCS).

Independent variables. The primary independent variable of interest will be carotid-femoral pulse wave velocity (CFPWV). While considering additional tonometric measures, including forward wave amplitude, we will focus on CFPWV because it is a robust single representative measure of arterial stiffness and in order to minimize any penalty for multiple testing.

Analytical approach. We will perform initial descriptive analyses including unadjusted (as well as age-, sex, and race-adjusted only) analyses of the relations between CFPWV and the primary LV measures (GLS and GCS, separate models for each). We will then perform multivariable-adjusted regression analyses to examine the association of CFPWV with the primary LV measures (GLS and GCS, separate models for each), including adjustment for the following clinical covariates: age, sex, race, study site, body mass index, systolic blood pressure, diastolic blood pressure, anti-hypertensive treatment, diabetes, total/HDL cholesterol ratio, lipid lowering therapy, heart rate, smoking status, triglycerides, and prevalent cardiovascular disease (defined as coronary heart disease, heart failure, or prior stroke or transient ischemic attack). We will also adjust for the following echocardiographic covariates: LV mass, LV wall thickness, LV end-diastolic diameter, LV relative wall thickness (LV wall thickness divided by LV end-diastolic diameter), LVEF, and E’. For all models, we will use multiplicative interaction terms to assess for effect modification by age, sex, race, body mass index, blood pressure, diabetes, lipids, and smoking status. We will also test for effect modification by LV mass, relative wall thickness, LVEF, and E’. We will perform stratified analyses for covariates demonstrating significant effect modification.

Secondary analyses. We will repeat the analyses above for select tonometric measures other than CFPWV, including forward wave amplitude (which has been reported as an additionally informative measure of arterial stiffness in older study samples). We will also repeat the analyses above for measures of radial (and transverse) strain. Whereas LV relative wall thickness is a continuous measure of LV geometry, we will also consider conducting analyses using categorical definitions of LV geometry (i.e. normal, concentric remodeling, concentric hypertrophy, and eccentric hypertrophy), as previously defined. We will also consider repeating all analyses in the subset of individuals without prevalent cardiovascular disease.
Limitations and challenges. Because these analyses will be cross-sectional only, causal relationships cannot be inferred.

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 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.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)?

MS # 515 (Liao) Association of arterial stiffness and left ventricular hypertrophy

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/

12. 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.
References


