ARIC Manuscript Proposal #2016

PC Reviewed: 10/9/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
The relationship between left ventricular torsion, cardiac mechanics and geometry assessed by three-dimensional echocardiography in a community-dwelling elderly cohort: the ARIC study

b. Abbreviated Title (Length 26 characters):
LV torsion in relation to geometry

2. Writing Group:
Writing group members:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. CH **[please confirm with your initials electronically or in writing]**

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3. Timeline:
Analysis will begin once this manuscript proposal is approved. We anticipate preliminary analysis results for abstract submission to American College of Cardiology 2013 Scientific Sessions (November 2012). We anticipate manuscript completion approximately 3 months following abstract submission (January 2013).

4. Rationale:

LV twist and torsion, which characterize the wringing motion of the ventricle during systole due to contraction of helical myofibers[1,2], is an important feature of LV systolic function[3] that is not adequately captured by traditional two-dimensional measures such as LVEF[4]. However, the relationship between LV twist and alterations in LV shape and geometry has not been well defined, particularly among elderly community-dwelling individuals.

Concentric LV remodeling, characterized by a smaller LV lumen and increased LV wall thickness, is associated with several cardiovascular co-morbidities such as diabetes and hypertension. Both myocyte hypertrophy in response to increased LV wall stress and altered extracellular matrix deposition are thought to contribute to these changes in cardiac morphology[5,6]. Speckle-tracking based myocardial deformation has emerged as an important imaging technique to characterize LV mechanics and individual components of systolic/contractile function (longitudinal, circumferential, radial, twist, torsion)[7,8]. This has substantially enhanced understanding of the changes in cardiac mechanics characterizing in various diseases, even at an early stage. LV twist and torsion, in particular, may be particularly useful in linking impaired systolic and diastolic performance. Indeed, our preliminary data from ARIC (MS#1953), in addition to recent published manuscripts,[9,10] suggest that concentric remodeling is accompanied by impaired longitudinal function despite preservation of LVEF. However, while LV concentric remodeling is associated with impaired longitudinal function, recent data from small single center studies suggest concomitant increases in LV circumferential function and twist, possibly compensating for longitudinal functional decline in order to maintain a normal LVEF[11,12]. In addition to being limited by small sample size and an inability to assess variability between key subgroups (gender, age, race/ethnicity), most previous studies were performed by using two-dimensional echocardiography, which is particularly limited in the assessment of the 3-dimensional wringing motion of the left ventricle. Advances in 3D echo imaging acquisition and analysis allow for assessment of LV deformation – including twist and torsion –based on a 3D computation model[13,14], which theoretically may provide more comprehensive and detailed information than 2D echo.

5. Main Hypothesis/Study Questions:

We hypothesize that among elderly persons without prevalent heart failure, greater LV concentric remodeling will be associated with reduced longitudinal strain but higher LV twist and torsion, with preserved measures of chamber-level function (cardiac output and LVEF)

To test the hypothesis, we will investigate the following specific aims:

1. Determine the association between 3D measures of LV mechanics (longitudinal strain, circumferential strain, twist) and LV geometry (defined by relative wall thickness, LV mass index, and LV mass-to-volume ratio), and explore whether these relationships vary significantly by gender, race/ethnicity, or age.
2. Determine the relationship between LV twist, LV untwist, and measures of LV diastolic function (assessed by mitral annular early relaxation velocity (E'), diastolic

strain rate, early mitral filling velocity (E wave)/late filling velocity (A wave) ration, E wave/E' ratio, and LA volume index).
3. Explore the association between 3D echo measures of LV mechanics and serum biomarkers of myocardial stress (NT-proBNP) and injury (high sensitivity troponin T)

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:
This will be a cross-sectional analysis of the first 1,000 ARIC Visit 5 echocardiograms with analyzable 3D data without prevalent heart failure.

Eligibility/exclusion:
Key inclusion criteria include available 3D volumetric data of good quality. Participants with suboptimal 3D image quality, atrial fibrillation at the time of echocardiography, a history of heart failure, or missing data for key clinical data will be excluded.

Key variables of interest:

1. Echocardiographic variables (visit 5 3D echo) of LV structure (wall thickness, relative wall thickness, systolic and diastolic diameters and volumes), LV systolic function (LVEF, stroke volume, cardiac output), deformation (longitudinal strain, circumferential strain, twist, torsion) and diastolic function (E wave, A wave, E wave deceleration time, TDI E', and LAVi) from visit 5 2D echo.
2. Laboratory values (at Visit 5): high sensitivity troponin T, NT-proBNP, serum albumin and creatinine, urine albumin and creatinine, hemoglobin and hematocrit, glucose, hemoglobin A1C, total cholesterol, triglycerides, HDL, LDL
3. Clinical covariates (at Visit 5): age, gender, race/ethnicity, height, weight, blood pressure, heart rate, history of hypertension, diabetes, dyslipidemia, coronary artery disease, prior MI or revascularization procedure, prior stroke or TIA, peripheral arterial disease, heart failure, prior hospitalization for heart failure

Methods of 3D Volume/Mass and various systolic/contractile deformation measure:
3D echocardiography was performed using a Philips ultrasound system with full-volume electrocardiogram (ECG)-gated 3D datasets acquired from the apical positions with a matrix array 2.5-MHz 3D transducer. During one breath-hold, the depth and sector width were adjusted to minimize the value as much as possible for optimal spatial and temporal resolution of the entire LV within the pyramidal volume. In the tissue harmonic mode, 3-4 wide-angled acquisitions were made consisting of 4 wedge-shaped sub-volumes acquired over 4 consecutive cardiac cycles and automatically integrated into a wide-angle (70 x 70°) pyramidal dataset with the highest frame rate achievable (20-26 Hz in our study). The data were stored and transferred for off-line analysis. Among consecutive acquisitions, the most optimal image dataset was then chosen by an experienced cardiologist for subsequent analysis.

For image analysis, the epicardial and endocardial borders at end-diastole for the 2- and 4 chamber views were automatically traced using the TomTec software (**Image-Arena** VA, **TomTec**, Corp), with minimal manual adjustment by the same experienced investigator blinded to clinical information. 3D echocardiographic measures of left ventricular end diastolic volume (LVEDV), left ventricular end systolic volume (LVESV), LVEF, 3D myocardial volume, and LV mass will be measured using the QLab software (PHILIPS, 3D Quantification Advanced) Global 3D strain, 3D longitudinal strain (LS), 3D radial strain (RS), 3D circumferential strain (CS), and LV twist will be analyzed using the TOMTEC software.

Summary of data analysis:

Continuous data will be shown as mean and standard deviation (SD) and categorical data expressed as the frequency and proportion of prevalence in all subjects. We will first examine whether there is obvious baseline demographic data selection bias between those enrolled in the 3D study and those not enrolled. Then, we will divide the cohort into 4 categories based on LV geometry (LV mass-volume ratio), and measures of LV systolic function, diastolic function, and deformation (including twist) will be determined , and a trend test performed across ordered geometric groups. Specifically, Table 1 will evaluate demographic data/clinical covariates, in addition to levels of NT-proBNP and high sensitivity troponin T, by LV geometry category. Table 2 will focus on conventional 2D echocardiographic measures, including LV wall thickness, diameter, volume (both systolic and diastolic), LA volume, LV mass as well as Doppler Information and myocardial tissue Doppler (TDI) data provided. Table 3 will focus on all myocardial strain components. Trend test will be performed across these LV geometry subgroups.

To evaluate the adjusted relationship between LV geometry and deformation measures, univariable/bivariate regression models between various LV deformation components and LV geometry, clinical covariates, biochemical data, will be developed. Those potential confounders from univariable analysis ($p<0.1$) will be chosen to enter the multivariable analysis. To evaluate for a differential relationship between LV geometry and LV deformation among relevant subgroups (gender, age, race/ethnicity), interaction terms will be entered into the mutlivariable model and a interaction term p value <0.05 will be interpreted as indicating significant effect modification.

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)?

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.cscc.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.

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