1.a. Full Title:
Comparison of left ventricular torsion mechanics derived from two-dimensional and three-dimensional echocardiography in a community-dwelling elderly cohort: The ARIC study

b. Abbreviated Title (Length 26 characters):
Comparison of LV twist between 2D and 3D echocardiography

2. Writing Group:
Writing group members:
Chung-Lieh Hung, MD, Amil Shah, MD, Susan Cheng, MD, Dalane Kitzman, MD, OTHER ECHO CMT MEMBERS, Scott D. Solomon, MD

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]

First author: Hung, Chung-Lieh MD
Address: Brigham and Women’s Hospital, 75 Francis Street, Boston, MA 02115

Phone: 886-2-2543-3535 ext. 2456 Fax: 886-2-2543-3535 ext. 2459
E-mail: jotaro3791@gmail.com

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).
Name: Amil M. Shah, MD MPH
Address: Brigham and Women’s Hospital, 75 Francis Street, Boston, MA 02115

Phone: 617-525-6733 Fax: 617-582-6027
E-mail: ashah11@partners.org

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 6 months following abstract submission (March 2013).

4. Rationale:
Left ventricular (LV) twist refers to the net difference of the clockwise and counterclockwise wringing rotation from LV apex and base respectively, whereas LV torsion is LV twist normalized to LV long-axis distance. This wringing motion represents a major component of cardiac systolic deformation due helical myofibers contraction, but is not adequately captured by traditional measures of systolic function such as left ventricular ejection fraction (LVEF)\textsuperscript{1,2,3}

Previously, LV twist was assessed largely by magnetic resonance imaging (MRI)\textsuperscript{4}, biplane cine angiography\textsuperscript{5} or even sono-micrometry\textsuperscript{6}. However, these modalities are inconvenient, expensive, and are not widely or broadly applicable. Advances in echocardiographic myocardial deformation imaging by speckle-tracking in recent years has allowed quantification of LV twist by using gray scale, two-dimensional ultrasonic images\textsuperscript{7}. However, important limitations exist to the assessment of LV twist and torsion by 2D echocardiography: (1) out-of-plane motion of LV basal short axis view, (2) variability in the ventricular level at which the LV apical short axis view is obtained, and (3) measurement of basal and apical rotation from separate cardiac cycles.

Recent advances in three-dimensional (3D) echocardiography imaging acquisition and post-processing have made assessment of LV twist and torsion using 3D echo data feasible.\textsuperscript{8,9} 3D echocardiography theoretically may be superior to 2D assessment as: (1) apical and basal rotation is assessed from the same 3D volumetric dataset, and (2) greater uniformity in the basal and apical levels interrogated can be achieved. Therefore, 3D-based imaging may provide a more accurate, though similarly feasible, technique to assess LV torsion and twist as 2D-based measures, although limited data exists regarding their comparability in a large group of elderly persons in a community based cohort.

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

3D-based LV speckle-tracking measures of LV torsion and twist will be comparable to 2D-based measures. The correlation of LV rotation between 3D echo based measures and 2D echo based measures will be greater at the apical level than the basal/mitral valve level.

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

1. To determine the variability and comparability of LV twist and torsion assessed by 2D- and 3D-based methods;
2. To compare the variability and comparability of 3D echo and 2D echo assessments of the individual LV apex and basal layer rotation (measured in degrees).

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, comparing the 2D- and 3D-based LV twist measure, from ARIC Visit 5 echocardiograms with analyzable 3D dataset for about 300 subjects
Eligibility/exclusion:
Key inclusion criteria include subjects with both available 2D loops and 3D volumetric data of good quality. Participants with suboptimal 3D image quality, atrial fibrillation at the time of echocardiography, 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 function (LVEF, stroke volume, cardiac output). Echocardiographic variables of LV diastolic function (E wave, A wave, E wave deceleration time, TDI E’, and LAVi) for visit 5 2D echo.
2. Clinical covariates (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 2D- and 3D-based LV twist measure
2D echocardiography was performed by using a Philips ultrasonic system equipped with 2.5-MHz 2D transducer. Standard 2D image loops including apical views and three short-axis layers were all acquired. Ventricular 2D image loops were saved in DICOM format, which may render commercialized speckle-tracking software (2D Cardiac Performance. Analysis©, TomTec, Germany) analysis. The changes of rotational degree with time from both LV basal and apical layers by speckle-tracking methods will be stored on Excel sheet, and extracted for computation of rotational differences between these two short-axis planes based on the same timing points.

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 (4D LV Analysis©, TomTec, Germany) 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/torsion will be analyzed using the TOMTEC software.

Summary of data analysis:

Continuous data were shown as mean and standard deviation (SD) with categorical data expressed as the frequency and proportion of prevalence in all subjects. Feasibility of both 2D and 3D echo based twist/torsion assessments will be reported as the percent of total studies analyzable. Intra- and inter-reader variability for both 2D and 3D echo based twist/torsion assessments will be reported using Bland-Altman analysis, including bias, limits of agreement coefficient of variation, and intraclass correlation coefficient. Similarly, agreement between 2D and 3D echo based twist/torsion assessments, and component measures of LV apical rotation and basal rotation, will be reported using a similar Bland-Altman analysis and intraclass correlation coefficient.

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_DÑA = “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.csc.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.
References Cited