1.a. Full Title:
Feasibility and reference values for left ventricular size, function, and deformation in an elderly cohort determined by 3D echocardiography: the ARIC study

b. Abbreviated Title (Length 26 characters):
3D echocardiography: feasibility & reference values.

2. Writing Group:
Writing group members:
Amil Shah, MD, Chung-Lieh Hung, 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. ___AS__ [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 6 months following abstract submission (March 2013).

4. Rationale:
Three-dimensional speckle tracking echocardiography (3D echo) allows for assessment of left ventricular volumes, ejection fraction, strain, twist, and torsion from a volumetric dataset acquired over several – typically four – cardiac cycles. Compared to standard 2D echo, 3D imaging does not face limitations of foreshortening, off-axis imaging, and the use of measurements from different cardiac cycles to derive values like LV volumes, ejection fraction, twist and torsion. Theoretically, this is particularly advantageous when assessing the complicated 3D wringing motion of the heart often characterized as twist and torsion. 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. However, 3D echo image acquisition is also more technically demanding, less widely available, and lower resolution than 2D imaging.

Despite the theoretical promises of 3D echo, little data is available regarding the feasibility of acquiring interpretable data in a free living cohort of unselected elderly individuals, or how this feasibility varies by gender and race/ethnicity. In addition, several small in vitro and human studies have assessed the comparability of 3D measures of LV volumes and EF against 2D echo and MRI, and the comparability of 3D torsion against sonomicrometry and in vitro assessment of rotation. However, little data is available regarding reference ranges for measures of LV size (volumes) and function (EF, strain, twist, and torsion) derived by 3D speckle-tracking echo, and how these reference values may vary by gender, age category, and race/ethnicity in the elderly.

5. Main Hypothesis/Study Questions:
3D speckle-tracking echocardiography will be feasible in the majority of persons in an unselected free living cohort of unselected elderly individuals, with obesity and pulmonary disease associated with unusable 3D imaging data. We further hypothesize that reference limits for 3D speckle tracking-based measures of LV size and function will vary significantly by gender, age, and race/ethnicity.

To test these hypotheses, we will investigate the following specific aims:

1. Determine the feasibility and clinical predictors of acquiring adequate quality 3D echo data for 3D speckle tracking analysis in an unselected cohort of free living elderly individuals.
2. To establish reference limits for 3D speckle-tracking echo-based measures of LV size (LV volumes at end-diastole and end-systole) and LV function (EF; global strain; longitudinal, circumferential, and radial strain; twist; torsion), determine whether/how these reference limits vary by gender, age, and race/ethnicity, and identify key clinical correlates of these measures in healthy elderly population.

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 3,000 3D echocardiograms from ARIC Visit 5.

Eligibility/exclusion:
Key inclusion criteria include 3D echo data acquired during ARIC visit 5.

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).
2. Clinical covariates (Visit 5): site, performing sonographer, 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 for 3D Echo Data Acquisition
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. When consecutive acquisitions were available, the most optimal image dataset was then chosen by an experienced cardiologist for subsequent analysis. 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:
For Specific Aim 1, the feasibility of 3D echo based assessments will be reported as the percent of total studies analyzable. To help indentify characteristics associated with feasibility, Field center, performing sonographer, and participant demographic and clinical characteristics will be determined based on feasibility of 3D echo (feasible or not) and compared using a t-test for normally distributed continuous variables and a Fischer’s exact test for categorical variables.
For *Specific Aim 2*, healthy participants will be selected from those with analyzable 3D data. ‘Healthy’ will be defined as (exclusion listed in hierarchical order): no hypertension (excluded in history of hypertension or use of antihypertensive medications or visit 5 SBP>140 mmHg or visit 5 DBP>90 mmHg), non-obese (excluded if visit 5 BMI>30), no diabetes (excluded if history of diabetes or on anti-diabetic medications or fasting glucose ≥126, no renal insufficiency (excluded if eGFR≤60 or proteinuria), no atrial fibrillation (excluded if history of atrial fibrillation or AF on visit 5 ECG or AF on visit 5 echocardiogram), no significant valvular heart disease (excluded if moderate or greater valvular lesion), and no known coronary heart disease, stroke, peripheral arterial disease, or heart failure.

To define reference limits within this ‘healthy’ group, we will summarize the distribution of 3D echo measures of LV size and function and determine the 2.5\textsuperscript{th}, 50\textsuperscript{th}, and 97.5\textsuperscript{th} percentile estimates. Similar analyses will be performed in subgroups stratified by: gender, age in 10-year increments, and race/ethnicity (white versus black). Given the anticipated limited sample size in some of these subgroups (blacks in particular), we will also determine reference limits based on linear quantile regression analyses.\textsuperscript{10,11}

Finally, we will employ multivariable linear regression to identify participant demographic and clinical characteristics associated with key advanced 3D echo measures of cardiac function (strain, longitudinal strain, twist, and torsion) within this ‘healthy’ group. Covariates included in these regression models will include: age, gender, race, BMI, heart rate, SBP, DBP (all at visit 5).

7.a. Will the data be used for non-CVD analysis in this manuscript?  ____ Yes  _V_ 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  _V_ 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

___V___ 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  ___V__ 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

1 Monaghan MJ. Role of real time 3D echocardiography in evaluating the left ventricle. *Heart* 2006;92:131-6.