1.a. Full Title: The relationship between concentric remodeling and left ventricular function – A preliminary analysis from the ARIC study

b. Abbreviated Title (Length 26 characters):
Concentric remodeling and LV function in ARIC

2. Writing Group:
Writing group members: Amil M Shah, Kunihiro Matsushita, Dalane Kitzman, Ervin Fox, Suma Konety, Scott D. Solomon; Others welcome.

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. Preliminary results will be submitted to the American Heart Association 2012 Annual Scientific Sessions (June 2012). Anticipate manuscript completion in approximately the following 3 months.

4. Rationale:
The association between cardiac enlargement and heart failure (HF) has long been recognized, with a fundamental relationship existing between myocardial wall stress, ventricular hypertrophy, and chamber enlargement.\(^1,2\) Pressure overload is associated with sarcomere replication in parallel and increased wall thickness-to-chamber radius ratio (concentric remodeling), allowing for normalization of left ventricular (LV) peak systolic meridional wall stress.\(^3\) Aging is associated with increased concentric remodeling.\(^4\) Indeed, preliminary data from echocardiography in ARIC Visit 5 demonstrate concentric remodeling or hypertrophy in 47% of participants. Concentric remodeling, even in the absence of frank hypertrophy, is clinically relevant. While increased LV volume\(^5\) and LV mass\(^6,7,8\) are both powerful predictors of cardiovascular morbidity and mortality, and the relationship between LV mass and chamber size (LV mass to volume ratio or relative wall thickness), provides incremental prognostic information.\(^9,10,11\)

Concentric remodeling has been associated with impaired diastolic function and increased diastolic LV stiffness.\(^12\) Indeed, as reflected in recent guidelines, heart failure with preserved ejection fraction (HFpEF) is believed to be primarily a disorder of diastolic function, characterized by preserved to decreased LV cavity size and frequent concentric remodeling.\(^13\) Importantly, several studies also suggest that concentric remodeling can mask impairments in myocardial systolic function despite preserved or even increased chamber-level measures of LV systolic function, such as ejection fraction and fractional shortening.\(^14,15,16\) More recent data using 2D speckle tracking indicate that progressive concentric remodeling is associated with reduced longitudinal deformation despite normal LVEF and increased circumferential deformation.\(^17,18\) This emerging data using myocardial deformation imaging suggest a distinct pattern of LV dysfunction in conditions predisposing to HFpEF, such as hypertension and diabetes, characterized by impaired longitudinal systolic function with concomitant increase in circumferential systolic function, maintaining overall LVEF.\(^19,20,21\)

Importantly, the myocardial response to pressure overload appears to differ among women compared to men and among African Americans compared to whites. LV mass and volumes are consistently lower in women compared to men, even after adjustment for height or BSA,\(^22,23\) and women tend to have a higher LVEF for any given LV end-diastolic volume. Observational studies of LV pressure overload in the form of arterial hypertension\(^24,25\) and aortic stenosis\(^26\) demonstrate that women manifest an exaggerated hypertrophic response compared to men with greater preservation of systolic function.\(^27\) Data from the ARIC Jackson Heart Study demonstrate an impressively high prevalence of concentric hypertrophy (29%) and concentric remodeling (36%) in a middle aged community based cohort of African Americans,\(^28\) and comparative studies in non-hypertensive healthy subjects suggest that LV mass and RWT are higher in African Americans compared to whites.\(^29\) African Americans also appear to develop greater degrees of concentric remodeling\(^30\) and hypertrophy\(^31\) for a set degree of hypertension. Finally, the prognostic implications of LV remodeling on progression to symptomatic HF and its complications may differ in these two groups.\(^32,33\) However, whether the relationship between concentric remodeling and left ventricular systolic and diastolic function differs significantly in these populations is not well understood.
Echocardiography in the fifth visit of ARIC therefore provides a unique opportunity to assess the relationship between LV concentric remodeling and measures of LV systolic and diastolic function and to evaluate whether these relationships vary appreciably among women and African Americans.

5. Main Hypothesis/Study Questions:

We hypothesize that greater degrees of concentric remodeling will be associated with higher chamber-level measures of left ventricular systolic function (ejection fraction, fractional shortening) and higher circumferential deformation but lower longitudinal and radial deformation.

Specifically, we aim to:
1. Define the relationship between LV concentricity, reflected in the LV relative wall thickness (RWT), and:
   a. Left ventricular meridional and circumferential wall stress, estimated echocardiographically
   b. Chamber-level measures of LV systolic function (ejection fraction, fractional shortening) and ejection-phase measures of systolic function (stroke volume index, cardiac index, and stroke work)
   c. Measures of myocardial function and deformation in the following planes: (1) longitudinal [longitudinal strain, mitral annular systolic velocity], (2) circumferential [circumferential strain], and (3) radial [radial strain and mid-wall fractional shortening]
2. Determine whether the relationship between concentric remodeling and LV systolic myocardial mechanics varies by gender and race/ethnicity

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 ARIC Visit 5 echocardiograms analyzed with complete myocardial deformation imaging data.

Inclusion/exclusion criteria:
This analysis will include all ARIC participants undergoing echocardiography at Visit 5. Participants with missing data for key echocardiographic measures (LVEF, LV wall thickness, LV diameters, LV volumes, LV longitudinal, circumferential, and radial strain) will be excluded from this analysis.

Key variables of interest:
1. Echocardiographic variables (visit 5 echo) of LV structure (wall thickness, relative wall thickness, systolic and diastolic diameters and volumes), LV systolic
function (LVEF, fractional shortening, stroke volume, mid-wall fractional shortening, mitral annular systolic velocities, longitudinal strain, circumferential strain, radial strain), LV diastolic function (E wave, A wave, E wave deceleration time, TDI E’, and LAVi), and pulmonary artery systolic pressure

2. Laboratory values (visit 5): NT-proBNP, serum albumin and creatinine, urine albumin and creatinine,

3. 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, heart failure

Data analysis:
In addition to echocardiographic measures of LV function already being performed in ARIC, the following values will be derived from existing echocardiographic measures:

Fractional shortening (FS) = 100*(LVEDD – LVESD)/LVEDD

Mid-wall fractional shortening (MWFS) as described by Mayet et al. 34

Stroke volume (SV) = LVEDV – LVESV

Stroke volume index (SVI) = SV/BSA

Stroke work in g-m (SW) = 0.0136 x (SV) x (mean arterial pressure) [reference 15]

Stroke work per 100 g myocardium (SW/100 g) = SW/(LV mass/100) [reference 15]

Meridional wall stress in 10^3 dyn/cm^2
   = 0.334 x SBP x LVESD)/(ESPWT x (1 – ESPWT/LVESD))

   where SBP = systolic blood pressure, LVESD = LV end systolic dimension, ESPWT = end-systolic posterior wall thickness 35

Circumferential wall stress in mmHg
   = ((SBP x (LVESD/2))/ESPWT) x (1 – ((2 x (LVESD/2)^2)/LVESL^2))

   where LVESL = LV end-systolic length [reference 35]

Participants will be categorized into five categories based on quintiles of relative wall thickness. Clinical covariates, laboratory variables, and echocardiographic measures of LV structure, wall stress, systolic function, and diastolic function will be described by RWT category. Continuous data will be displayed as mean ± standard deviation if normally distributed. Categorical variables will be displayed as proportions. Association of RWT with echocardiographic measures of LV structure, wall stress, systolic function, and diastolic function will be assessed by trend test modeling RWT as a categorical variable and by Pearson correlation modeling RWT as a continuous variable. As measures of LV systolic function generally, and of myocardial deformation in particular,
are influenced by LV size and wall stress, associations of RWT with echocardiographic measures of LV function will also be assessed adjusting for LV end-diastolic volume and LV end-systolic wall stress in multivariable linear regression models. Similar analyses will be performed stratified by gender and by race/ethnicity (white, African American). To assess whether the observed relationships between LV concentric remodeling and systolic measures are significantly modified in these sub-groups, we will test for interaction between RWT and gender or race.

_Anticipated methodologic limitations:_

A major limitation for this analysis is the use of noninvasive estimates for invasive hemodynamics, which have inherently limited precision. However, these non-invasive estimators have been previous validated and invasive hemodynamic assessments in this population would not be feasible. Another limitation is the cross-sectional nature of this analysis, which limits our results to determining associations between LV concentric remodeling and measures of systolic function, and precludes conclusions regarding causality.

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

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.cscu.unc.edu/ARIC/search.php](http://www.cscu.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/](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

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11. Koren MJ, Devereux RB, CasalePN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med* 1991;114:345-52.


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