1.a. **Full Title:** Regional left ventricular deformation obtained by speckle tracking echocardiography in different risk groups and in different spectra of heart failure

b. **Abbreviated Title (Length 26 characters):** Regional deformation, Echo, risk groups, heart failure

2. **Writing Group:**
   Writing group members: Tor Biering-Sørensen, Amil Shah, Kotaro Nochioka, Maja Cikes, Brian Claggett [Others welcome], Scott D. Solomon

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __TBS__ [please confirm with your initials electronically or in writing]

**First author:** Tor Biering-Sørensen  
Address: Brigham and Women’s Hospital  
Cardiovascular Division  
75 Francis Street, PBB-1 North  
Boston, MA 02115

Phone: 617-901-2765  Fax: 617-582-6027  
E-mail: tor.biering@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: Scott D. Solomon  
Address: Brigham and Women’s Hospital  
Cardiovascular Division  
75 Francis Street  
Boston, MA 02115

Phone: 857-307-1960  Fax: 857-307-1944  
E-mail: ssolomon@rics.bwh.harvard.edu

3. **Timeline:** Analysis will begin following proposal approval with the aim of completing analysis and a manuscript within 6 months of data becoming available.
4. **Rationale:**

The aging population along with increasing rates of hypertension\(^1\), diabetes\(^2\), and obesity\(^3\) conspire to create a growing pool of individuals at particularly high risk for heart failure (HF) development. Hence, hypertension and diabetes become obvious targets for prevention, being two of the key risk factors for ischemic heart disease (IHD)\(^4\) and HF\(^5\). The burgeoning epidemic of these clinical entities emphasizes the need for rapid, cheap, and non-invasive diagnostic methods to identify high risk subjects with early myocardial deterioration so as to ensure that preventive therapy be initiated.

Studies have indicated that the echocardiographic technique of speckle tracking echocardiography enables detection of impaired myocardial performance in patients with hypertension\(^6,7\), diabetes\(^8,9\), and IHD\(^10\). Additionally, emerging science using novel myocardial deformation imaging echocardiography suggests a distinct pattern of left ventricular dysfunction in conditions (such as hypertension and diabetes) predisposing to HF. These studies suggest that early dysfunction is characterized by impaired longitudinal systolic function with concomitant increase in circumferential systolic function, thereby maintaining overall LVEF in spite of an ailing myocardium\(^11-15\). However, previous studies using speckle tracking echocardiography to identify subclinical cardiac dysfunction have focused on the global measures of myocardial function such as global longitudinal strain (GLS) and global circumferential strain (GCS). Nevertheless, both GLS and GCS are based on averaging regional differences in deformation amplitude, why the information we can gain from regional function may be diluted in the process. Furthermore, the curvature of the ventricle increases from the apex to the base of the heart and also from the lateral to the septal wall. Regions with more flattened structure, and thus higher radius of curvature, entails an intrinsically higher wall stress\(^16,17\). These discrepancies in the workload the myocytes perform, caused by regional anatomical differences, may result in regional dissimilarities in how they are affected by different risk factors such as hypertension and diabetes. Additionally, if regional myocardial deformation by speckle tracking echocardiography proves able to detect subclinical myocardial dysfunction in persons in the community, its diagnostic usefulness would be consolidated and the integration of speckle tracking into routine echocardiographic examination would be further motivated; particularly so if regional myocardial deformation obtained by speckle tracking echocardiography provides information incremental to that of conventional echocardiography.

Furthermore, if we can use the novel regional myocardial deformation measures to characterize regional myocardial impairments caused by different risk factors and identify persons in high risk of HF and characterize perturbations in regional cardiac function across the spectrum of HF (stages A to C and HF with preserved ejection fraction (HFrEF) to HF with reduced ejection fraction (HFrEF)), we will expand our understanding of the pathophysiology responsible for HF progression and gain insight for future therapeutic strategies. This is of the utmost importance, especially when considering the emerging HF epidemic in general and specifically in patients with HFrEF where the absence of a clear diagnostic definition in terms of an echocardiographic phenotype is the primary reason for the lack of an effective therapy in this patient category.

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

Hypothesis: Regional deformation measures in specific regions of the heart provide incremental information to global deformation measures, for diagnostic and prognostic purposes. This is
because global deformation measures dilute the information gained from subtle signs of regional cardiac impairment.

Specific hypothesis:

1. Impaired regional deformation measures are differently distributed according to different cardiovascular risk groups and diseases: Normal vs. diabetes, hypertension, impaired kidney function, IHD and HF.
2. Impaired regional deformation measures are differently distributed across the spectrum of HF: From normal, stages A to C and HFpEF to HFrEF.
3. Regional deformation measures are differently associated with cardiac biomarkers (NT-proBNP, high sensitivity troponin T), blood glucose, Hb1Ac, blood pressure, eGFR and urine albumin.
4. Regional deformation measures provide incremental information to global deformation measures when predicting risk of future cardiovascular disease.

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 ARIC Visit 5 echocardiograms analyzed with complete myocardial deformation imaging data. Additionally, it will include the participants from the ARIC cohort from visit 5, who have acceptable echocardiography image quality for 3D analysis.

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, global and regional longitudinal strain, global and regional circumferential strain, global and regional 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, high sensitivity troponin T, 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:
Categorical variables will be compared via \( \chi^2 \) and continuous data will be compared between groups via a non-parametric trend test. P values < 0.05 will be considered significant. Participants will be stratified according to prespecified groups: Normal, diabetes, hypertension, impaired kidney function, IHD and HF. The distribution of regional deformation will be assessed in all the prespecified groups. Additionally, participants will be stratified according to prespecified HF groups: Normal, stages A to C and HFpEF and HFrEF. Univariable and multivariable linear and logistic regression analysis will be used to assess associations between regional deformation as continuous and categorical variables and clinical and echocardiographic characteristics. Adjustments for differences in clinical characteristics (based upon P <0.05 and/or clinically important covariates) will be performed. Effect modification by gender and LVEF will also be tested.

Limitations:
A primary limitation is the cross-sectional nature of this analysis, which limits our results to determining associations between regional deformation and clinical characteristics, 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 ICTDER 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)?

Amil M Shah, Kunihiro Matsushita, Dalane Kitzman, Ervin Fox, Suma Konety, Scott D. Solomon; Others welcome. The relationship between concentric remodeling and left ventricular function – A preliminary analysis from the ARIC study. MS Proposal #1953.
*This proposal focuses on global but not regional deformation.

*Natalie Bello, Susan Cheng, Gabriela Querejeta Roca, Amil Shah, Angela B.S. Santos, Deepak Gupta, Brian Claggett, June Stevens, Josef Coresh, Scott Solomon, OTHERS. The relationship between cardiac structure and function and obesity assessed by body composition contrasted with anthropomorphic measures. MS Proposal #2228.

*Hicham Skali, Amil Shah, Deepak Gupta, Susan Cheng, Brian Claggett, David Aguilar, Natalie Bello, Kunihiro Matsushita, Orly Vardeny, Elizabeth Selvin, Scott Solomon, Others welcome. Cardiac structure and function across the dysglycemia spectrum in a bi-ethnic older population: the ARIC study. Proposal #2119.

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.csc.unc.edu/aric/forms/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.csc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.
References


