1.a. Full Title: Changes in left ventricular function in African–Americans over time: a combined analysis from ARIC and JHS.

b. Abbreviated Title (Length 26 characters): African Americans and echo

2. Writing Group:
   Writing group members: Deepak K. Gupta, Amil M. Shah, Ervin Fox, Ken Butler, Tom Mosley, Others Welcome, Herman Taylor, Scott D. Solomon.

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

**First author:** Deepak K. Gupta  
**Address:** Vanderbilt University Medical Center  
Vanderbilt Heart and Vascular Institute  
2525 West End Ave, Suite 300  
Nashville, TN 37203

Phone: 616-936-2530  
Fax:  
E-mail: deepak.gupta@vanderbilt.edu

**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 and obtaining data, with the aim of completing analysis and submitting an abstract to a major cardiology meeting within 6 months. The subsequent aim will be to complete a manuscript within 1 year of data availability.
4. **Rationale:**

African Americans have an increased prevalence of cardiovascular risk factors, higher incidence rates of heart failure (HF), and worse prognosis compared to white patients. Nevertheless, most epidemiologic studies of cardiovascular disease, including the Framingham Heart Study and Olmsted County, Minnesota, have enrolled predominantly white participants. Consequently, cardiovascular disease in African-Americans remains relatively unexplored. In particular, longitudinal changes in cardiac structure and function in relation to cardiovascular disease are not well understood.

Moreover, the relationship between cardiovascular risk factors and cardiac structure and function in African-Americans is not clear. While coronary artery disease (CAD) is considered a leading etiology for heart failure, it appears to play a lesser role in African-Americans. This is despite a higher prevalence of cardiovascular risk factors, namely hypertension, diabetes mellitus, smoking, obesity, and renal dysfunction. This pattern of risk factors aligns with the description of the “typical” HFpEF patient identified in predominantly white cohorts. However, among African-Americans these clinical characteristics have also been associated with left ventricular systolic dysfunction and lower ejection fraction. Moreover, left ventricular hypertrophy (LVH), another major risk factor for HF, is highly prevalent among the general African-American population and is related to hypertension, diabetes mellitus, and obesity. Both eccentric and concentric patterns of hypertrophy have been related to systolic and diastolic dysfunction. Together these data demonstrate that the relationship between clinical risk factors and cardiac structure and function in African Americans is not well understood, making clarification of these associations an unmet need.

Recently, sensitive measures of cardiac function, including myocardial strain and strain rate from speckle tracking echocardiography, have been validated. These parameters have revealed abnormalities in left ventricular systolic function even in the setting of preserved ejection fraction. Importantly impaired longitudinal systolic strain has been associated with adverse outcomes, independent of left ventricular ejection fraction and clinical risk factors.

Therefore, we aim to describe changes in cardiac structure and function over time in a community dwelling cohort of African-Americans. The Atherosclerosis Risk in Communities study (ARIC) and Jackson Heart Study (JHS) are well suited to address outstanding and unresolved questions regarding changes in cardiac structure and function over time in African Americans. The JHS was initiated in 2000 with 5,301 participants enrolled, of whom 30% were also ARIC participants. During JHS visit 1 (2000-2004), participants underwent transthoracic echocardiography as well as collection of data regarding cardiovascular disease. Given the overlap between JHS and ARIC participants, we anticipate that approximately 1000 participants will have echocardiographic data from both JHS visit 1 and ARIC visit 5 (2011-2013). Therefore, we anticipate that approximately 800-1000 participants from ARIC visit 5 will also have echocardiograms from JHS visit 1. Together, longitudinal data from 2 time points regarding cardiac structure and function, along with detailed information pertaining to cardiovascular disease and risk factors, provide the unprecedented and unparalleled opportunity to examine cardiovascular disease in African Americans.

5. **Main Hypothesis/Study Questions:** The primary objective is to describe changes in cardiovascular risk factors and cardiac structure and function in African-Americans over time.
Aim 1: To describe clinical characteristics and the prevalence of cardiovascular risk factors at each of the two time points.

Aim 2: To quantify left ventricular systolic strain and diastolic strain rate at each of the two time points.

Aim 3: To describe the frequency and correlates of change in left ventricular systolic strain and diastolic strain rate over time.

Aim 4: In a subset of JHS visit 1 echocardiograms, to quantify standard measures of cardiac structure and function in the Brigham and Women’s echocardiographic core lab to ensure comparability of measures ascertained from different reading centers.

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).

This will be a longitudinal study of African Americans participating in both ARIC and JHS who underwent transthoracic echocardiography during JHS visit 1 and ARIC visit 5. To be included in the analysis participants must have undergone echocardiography in both of these visits and have data available regarding left ventricular wall thickness and dimensions.

As speckle tracking was not performed on the JHS visit 1 echocardiograms, these studies will be sent to the Echocardiographic Core Lab at Brigham and Women’s Hospital, where 2D speckle tracking analysis will be performed offline following the procedures utilized for ARIC visit 5. In a subset of JHS visit 1 echocardiograms, standard features of cardiac structure and function, including but not limited to LV size, wall thickness, volumes, ejection fraction, diastolic function, left atrial size/volumes, and right ventricular size and function will be measured in the echocardiographic core lab at Brigham and Women’s Hospital. This is to ensure comparability of measurement techniques between JHS visit 1 and ARIC visit 5 as well as between reading centers for the JHS visit 1 studies. If needed, regression equations will be determined for each parameter of cardiac structure and function of interest at JHS visit 1 to account for differences in measurement technique between the Jackson and Brigham and Women’s reading centers.

Participants will first be categorized according visit date, i.e. JHS visit 1 and ARIC visit 5. Summary statistics for clinical characteristics and features of cardiac structure and function will be described at each of these visits.

Next, participants will be categorized according to change (increase, decrease, no change) in LV longitudinal systolic strain between JHS Visit 1 and ARIC visit 5. Change in LV longitudinal systolic strain will be assessed as an absolute difference between echocardiograms of ≥ 1 standard deviation. Summary statistics for baseline clinical characteristics and features of cardiac structure and function will be calculated. Multivariate logistic regression analyses will then be performed to identify clinical and echocardiographic characteristics associated with change in LV longitudinal systolic strain. Interval cardiovascular events, i.e. myocardial infarction and heart failure, will be included in adjusted models as well.

Clinical characteristics and echocardiographic cardiac structure and function will be compared across groups based upon data variables collected at JHS visit 1 and ARIC visit 5. In particular, clinical variables to be evaluated include: age, gender, comorbidities, such as hypertension, diabetes, dyslipidemia, smoking status, coronary heart disease, stroke/TIA,
peripheral arterial disease, atrial fibrillation/flutter, obesity, chronic kidney disease, anemia, COPD, asthma, and alcohol use; electrocardiographic left ventricular hypertrophy and QRS duration; heart rate, blood pressure (systolic, diastolic, mean arterial, and pulse pressure), height, weight, body mass index, body surface area, waist to hip ratio; creatinine, WBC count, hemoglobin, red cell distribution width, glucose, and lipids. Echocardiographic variables to be evaluated include: left atrial size, left ventricular (LV) size, aortic root dimension, LV fractional shortening and ejection fraction, valvular disease, regional wall motion abnormalities, LV wall thickness, LV mass, LV geometry, LV stroke volume and cardiac output, Doppler mitral inflow E and A wave peak velocities, and E/A ratio.

Categorical variables will be compared via χ2 or Fischer exact test, while continuous data will be compared between groups via non parametric trend test. P values < 0.05 will be considered significant. Univariable and multivariable logistic regression analysis will be used to assess for associations between clinical characteristics and cardiac structure and function (independent) and the primary outcome of change in LV longitudinal systolic strain (dependent). Adjustments for differences in clinical characteristics (based upon P <0.05 and/or clinically important covariates) will be performed. Analyses will be repeated for speckle tracking derived measures of diastolic function.

Several limitations should be noted. Measurements of cardiac structure and function were measured at different time points by different core labs. Therefore, measurement bias may confound results. To assess for measurement bias, a subset of the JHS visit 1 echocardiograms will be re-analyzed in the echocardiography core lab (Brigham and Women’s Hospital) for ARIC visit 5. Furthermore, measurement techniques of cardiac structure and function have varied over time as newer techniques became available. For example, Tissue Doppler based measurements of left ventricular diastolic function were not obtained during JHS visit 1. Therefore, the analysis will be limited to those features of cardiac structure and function that could be measured. Finally, there will be both survivor and selection bias regarding those included in the study population; namely to be included, participants at JHS visit 1 must have survived and undergone echocardiography at ARIC visit 5. The sickest patients likely did not survive the approximate 10 year time span or may have been too ill to present for echocardiography at ARIC visit 5.

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?
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 ___ 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/

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.cscc.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

