ARIC Manuscript Proposal #2384

PC Reviewed: 6/10/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Cardiac and Brain Structure and Function Associations: The ARIC Study

b. Abbreviated Title (Length 26 characters):

2. Writing Group: Rebecca Gottesman (first; corresponding), Scott Solomon (last), Thomas Mosley, Michael Griswold, C. Cristina Quarta, Others welcome

Writing group members:

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

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3. Timeline: Data analysis and manuscript preparation are expected to be completed within 3-6 months following manuscript proposal approval.

4. Rationale:

Heart failure (HF) is a significant public health problem, with over 5 million individuals in this country having HF and with estimated costs of acute and chronic management of HF nearing $35 billion.[1] Although HF patients may have other organs adversely impacted during their disease course, the impact of HF on the brain is less well understood.

Patients with HF can develop cardioembolic stroke, either directly related to the reduced ejection fraction or related to a secondary arrhythmia. In addition, there may be neurologic injury, either transient or more permanent, from hypoperfusion related to this reduced cardiac output. Studies have shown that cardiac patients with low EF may have lower cognitive performance,[2 3] but whether this extends to individuals without symptomatic disease and with relatively small reductions in EF, as well as newer and more sensitive measures of cardiac function, such as longitudinal strain, is poorly studied.

White matter changes in the brain, also called white matter hyperintensities (WMH) or leukoaraiosis, are associated with long-standing hypertension, [4,5] which is itself seen in many patients with HF. Some studies, however, have suggested that this leukoaraiosis may be caused at least partially by hypoperfusion to these cortical border zones. Cortical watershed microinfarcts have been described in human autopsy series of subjects with Alzheimer's disease (AD), suggesting a possible mechanism of hypoperfusion.[6,7] Low cerebral blood flow is found in patients with early dementia, using both arterial spin-labeling[8] and transcranial doppler.[9] These data support a causative, rather than reactive, role of hypoperfusion in the development of dementia and cognitive impairment. It is plausible that reduced cardiac ejection fraction, even only to a mild degree, could

therefore contribute to the development or progression of leukoaraiosis, through a mechanism of hypoperfusion to the deep white matter. In patients with HF, more severe leukoaraiosis was identified in patients with reductions in cerebral blood flow velocity by transcranial Doppler,[10] and leukoaraiosis has been identified in the regions most pooryly perfused among patients with reduced cardiac output.[11] In addition, reduced cardiac index has been associated with reduced gray matter volumes- specifically, total gray matter volume.[12,13] Because atrophy (often measured by reductions in gray matter volume) is associated with the progression from normal cognition to mild cognitive impairment (MCI) and ultimately dementia,[14] it is plausible that this may be another mechanism by which HF and reduced cardiac function might increase risk of MCI and dementia, including AD.

If even mild (subclinical) changes in cardiac structure or function are associated with long-standing subclinical evidence of cerebral injury, this would point to not only a potentially modifiable target that could lead to prevention of cognitive impairment and dementia, but also would point to an end organ that needs to be followed in patients with HF. Because reduced cardiac function and changes in cardiac structure are highly influenced by underlying vascular risk factors, which in turn are important risk factors for structural brain changes (both vascular, such as leukoaraiosis and silent infarcts, as well as neurodegenerative, such as reductions in brain volumes), it is critical to explore an association between cardiac structure and function and brain structure with adequate evaluation of potential confounders of this association, which we think is possible in the ARIC study.

5. Main Hypothesis/Study Questions:

The primary hypothesis is that markers of abnormal cardiac structure and function will be associated with more evidence of brain imaging abnormalities- specifically, more white matter hyperintensities (leukoaraiosis), more silent infarcts, and smaller gray matter volumes, and that this association will be independent of other vascular risk factors.

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: Cross-sectional analysis (visit 5/ ARIC-NCS). Participants of the ARIC-NCS study who completed brain neuroimaging (who completed stage III) will be included in the analysis. We anticipate that all participants who completed stage III also completed the echocardiogram in stage I but will exclude anyone missing echocardiogram data.
Inclusion: Any participant who completed brain MRI in stage III and echocardiogram in stage I of ARIC-NCS.
Exclusion: Participants with known clinical history of stroke prior to the ARIC-NCS visit. We will include these subjects in a secondary analysis, but they will be excluded in the primary analysis since it focuses on subclinical heart and brain changes.
Outcome: Brain MRI findings: a) evidence of subclinical cerebrovascular disease: infarcts (cortical; subcortical); volume of white matter hyperintensities (standardized to total intracranial volume); microhemorrhages. And b) evidence of neurodegenerative disease: gray matter volumes (total gray, separate cortical lobal volumes, hippocampal volumes, AD signature region volumes)
Variables of interest: Markers of cardiac structure and function; covariates assessed at visit 5 (SBP, age, diabetes, smoking status, cholesterol, BMI, race/center, education) or via surveillance prior (for exclusions: prior history of adjudicated clinical stroke). Echocardiographic measures of cardiac structure and function (collected at visit 5) will include: standard 2D evaluation (left ventricular (LV) size, wall thickness and mass, LV geometry, left atrial size and volumes, aortic root dimension, valvular disease, LV ejection fraction, cardiac output and index, doppler mitral inflow), tissue Doppler imaging at septal and lateral wall levels (E', A' and S waves) and the more recent speckle tracking imaging derived measures of cardiac function (longitudinal, circumferential and radial strain and strain rate).

Limitations

The sample with available data at visit 5 likely represents a healthier sample than the larger visit 1 cohort. Because we are analyzing cross-sectional associations between variables from visit 5, we will not use methods such as inverse probability of attrition weighting to address this possible informative missingness due to dropout and death. We realize this may mean we are evaluating a healthier subcohort. We will weight the analyses based on the MRI sampling scheme (the analytic workgroup is finalizing plans

for this but currently planning primary analyses with weighting but without strata), which would weight the sample back to the stage I clinic visit population.

A subset of patients with cardiac structure and function abnormalities will not receive an MRI due to specific MRI exclusions: individuals with pacemakers, AICD's, or, for one of the field centers (Washington County, MD), certain cardiac stents, will be excluded from MRI, and the weighting schema doesn't specifically address this issue. We will consider differences in the two populations (stage 1 vs MRI/ weighted back to stage 1) in echo and MRI markers.

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 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 __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.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)?

MP 2119: Cardiac structure and function across the dysglycemia spectrum in a bi-ethnic older population: the ARIC study

MP 2227: Relationship of cardiac structure and function with cognitive performance: as study of the Atherosclerosis Risk in Communities (ARIC) study

MP 2218: Association of Blood Pressure Burden with Cardiac Structure and Function and Incident Heart Failure in the Community

MP 2351: Association of blood pressure with neurodegenerative and cerebrovascular changes on brain MRI

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes ____ No

11.b. If yes, is the proposal

X___ A. primarily the result of an ancillary study (list number* _ARIC NCS: 2008.06

___ 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.
Understood.

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.

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