ARIC Manuscript Proposal #2118

PC Reviewed: 4/9/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Characterization of cardiac and non-cardiac dysfunction in elderly persons with heart failure with preserved ejection fraction: The ARIC study

b. Abbreviated Title (Length 26 characters):
Characterization of HFpEF in ARIC

2. Writing Group:
Writing group members: Amil M Shah, Dalane Kitzman, Kunihiro Matsushita, Gerardo Heiss, Patty Chang, Laura Loehr, Sunil Agarwal, 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. Anticipate initial manuscript completion in approximately 3 months following proposal approval with final manuscript completion once Visit 5 is complete (9/2013).

4. Rationale:

Heart failure with preserved ejection fraction (HFpEF) is common, increasing in prevalence, and causes substantial morbidity, mortality, and resource utilization, particularly among the elderly.[1,2] Patients with HFpEF demonstrate pathophysiologic characteristics similar to patients with HF with reduced EF (HFrEF),[3] experience similar rates of HF re-hospitalization and functional decline,[4,5] and face a significantly higher risk of death compared to age-matched controls.[6,7] Despite multiple randomized controlled trials, no disease-specific therapy exists to improve prognosis in this heterogeneous syndrome.[8,9,10]

While the primary pathophysiologic abnormality in HFpEF is generally thought to be abnormal LV diastolic performance,[11,12,13] traditional noninvasive parameters of diastolic function are absent in approximately one-third of HFpEF patients and fail to reliably predict adverse events among HFpEF patients.[14,15] In addition, age-related changes in these structural and Doppler measures of diastolic function are well recognized,[16] and diastolic dysfunction is frequently detected in asymptomatic older persons, most of whom never develop HF. In the Olmsted County cohort, while diastolic dysfunction was detected in only 12% of participants 45-54 years old, it was noted in 71% of those ≥75 years old, although only 8.4% had clinical HF.[17] These findings suggest that, in the elderly in particular, mechanisms other than diastolic dysfunction may be operative in the transition to symptomatic HF despite preserved LVEF. Additional putative mechanisms include impairments in LV systolic function not reflected in EF, excessive systolic-ventricular and arterial stiffening,[18] pulmonary hypertension with abnormal pulmonary vascular resistance,[19] adverse cardiopulmonary interactions related to concomitant obstructive lung disease, altered fluid handling related to co-existing renal impairment, anemia, obesity, and deconditioning.[20]

Surprisingly little data exists directly comparing measures of cardiac and non-cardiac dysfunction in HFpEF versus matched asymptomatic persons, particularly those with co-existing cardiovascular co-morbidities and particularly among the elderly. A better understanding of the cardiac and non-cardiac measures that distinguish person with HFpEF from their asymptomatic peers matched on key clinical characteristics may provide additional insight into potential mechanisms contributing to the transition from at risk to symptomatic HF in the elderly. Detailed phenotyping of cohort participants in ARIC Visit 5 offers the unique opportunity to identify cardiac and non-cardiac organ dysfunction distinguishing symptomatic elderly persons with HFpEF from their asymptomatic counterparts with similar risk factors. In addition, this large biracial cohort is uniquely positioned to investigate gender and race/ethnicity-based differences in these relationships.

5. Main Hypothesis/Study Questions:

We hypothesize that, compared to age-, gender-, race/ethnicity-, and co-morbidity-matched asymptomatic persons, elderly persons with HFpEF will demonstrated more pronounced abnormalities both cardiac and non-cardiac function. Specifically, we hypothesize that HFpEF patients will demonstrate: (1) worse LV concentric remodeling, LV systolic deformation (assessed by strain), and diastolic function; (2) higher

pulmonary artery pressure and pulmonary vascular resistance; (3) greater arterial stiffness; (4) worse renal clearance and proteinuria, (5) greater airflow obstruction, and (6) worse anemia.

Specifically, we aim to:

1. Determine whether persons with HFpEF, compared to matched controls, demonstrate worse *cardiovascular* function in the following domains: (1) LV structure/concentric remodeling (volumes, wall thickness, mass); (2) LV diastolic function (TDI E', E/E' ratio, LAVi); (3) LV systolic deformation (longitudinal and circumferential strain); (4) pulmonary pressure and vascular resistance (TR jet velocity, PVR); and (5) arterial stiffness and ventricular-arterial coupling.
2. Determine whether persons with HFpEF, compared to matched controls, demonstrate more pronounced *non-cardiac* organ dysfunction in the following domains: (1) renal function (eGFR, proteinuria); (2) pulmonary function (FEV_1/FVR ratio); (3) hematologic function (hemoglobin, hematocrit); and (4) dysglycemia (Hemoglobin A_1C, glucose).
3. Determine the relative association of cardiac and non-cardiac dysfunction to the odds of having HFpEF in the Visit 5 population overall, and determine whether these relationships vary significantly 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 based on data collected at ARIC Visit 5.

Inclusion/exclusion criteria:

Inclusion criteria for the analysis include: (1) echocardiographic data at Visit 5 with a reading center determined LVEF≥50%; (2) spirometry, renal function, hematologic, and glycemia data at Visit 5.

Key variables of interest:

1. Echocardiographic variables (visit 5 echo): (1) LV structure (LV end-diastolic and end-systolic volumes and dimensions), wall thickness, relative wall thickness, and mass); (2) LV diastolic function (E wave, A wave, E wave deceleration time, TDI E', and LAVi); (3) LV systolic function (LVEF, mid-wall fractional shortening, longitudinal strain, circumferential strain); (4) pulmonary hemodynamics (estimated PASP based on TR jet velocity, PVR); and (5) right ventricular function (RVFAC, TDI tricuspid annular S')
2. Pulmonary function variables (visit 5): FEV_1, FVC
3. Renal function variables (visit 5): serum albumin and creatinine, urine albumin and creatinine, eGFR
4. Hematologic variables (visit 5): hemoglobin and hematocrit, glucose

5. Measures of dysglycemia (visit 5): hemoglobin A1C
6. 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, prior stroke or TIA, peripheral arterial disease, heart failure, prior hospitalization for heart failure

Data analysis:

Prevalent HFpEF cases in ARIC will be identified as ARIC participants with: (1) prevalent HF based on the recently approved 'specific' ARIC Heart Failure Committee Definition (based on information on prior adjudicated HF hospitalization, Physician health survey, and hospitalization prior to 2005 with ICD code 428.x in first position), and (2) an LVEF≥50% on Visit 5 echocardiogram. Two comparison groups will be identified: (1) a 'healthy' elderly group of participants without CV risk factors (hypertension, diabetes, obesity, atrial fibrillation, kidney disease, CHD, stroke, PAD, ≥moderate valve disease at Visit 5) matched for age, gender, and race/ethnicity; and (2) an 'at risk' population with CV risk factors matched for age, gender, race/ethnicity, and key co-morbidities (hypertension, diabetes, chronic kidney disease, CHD, atrial fibrillation, BMI).

To investigate cardiac and non-cardiac features differentiating HFpEF from healthy elderly, cardiac and non-cardiac functional measures will be compared between HFpEF group and matched 'healthy' group. Similarly, to investigate those features distinguishing HFpEF from asymptomatic elderly persons with similar HF risk factors, cardiac and non-cardiac functional measures will be compared between HFpEF and the matched 'at risk' group. Between-group comparisons will be performed using a Fisher's exact test for categorical variables, t-test for normally distributed continuous variables, and Wilcoxon rank sum test for non-normally distributed continuous variables.

To quantify the magnitude of association of cardiac and non-cardiac features with HFpEF, we will utilize univariate and multivariable logistic regression models. This portion of the analysis will be performed using the entire Visit 5 population (n ~ 6,000), with HFpEF status (yes/no) as the outcome variable. Cardiac and non-cardiac measures significantly different between HFpEF and comparison groups will be modeled separately as the primary predictors of interest. Multivariable models will adjust first for demographics then additionally for key HF risk factors. Area under the receiver-operator curve analysis will be employed to evaluate the ability of these measures to discriminate participants with from those without HFpEF, beyond information on demographics and key HF risk factors.

Anticipated methodologic limitations:

A major limitation for this analysis is its cross-sectional design. Ideally, we would be able to relate cardiac and non-cardiac measures characterizing HFpEF with (1) the risk of death or HF hospitalization among persons with HFpEF, and (2) the risk of incident HFpEF among participants without HF at Visit 5. However, this data will not be available for several years and future manuscript proposals will focus on this analysis. For prevalent HFpEF cases, LVEF assessment at Visit 5 may not reflect LVEF at the time of HF diagnosis or hospitalization. Indeed, in a subset of patients with HF in the context of reduced LVEF, LVEF subsequently recovers.[21] Among HFpEF cases with HF

hospitalization and chart abstraction by ARIC HF Classification Committee (occurring since 2005) and with abstracted hospitalization LVEF, we will determine the proportion with LVEF during prior hospitalization of <50%. We will compare Visit 5 measures among prevalent HFpEF participants with prior hospitalized LVEF<50% versus those without prior reduced LVEF and perform a sensitivity analysis restricted to those participants without prior reduced LVEF.

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? ____ 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)?

#1551: Sunil K. Agarwal, Patricia Chang, Richard Crow, Anita Deswal, Erwin Fox, Gerardo Heiss, Edgar Miller (response awaited), Wayne Rosamond, Eyal Shahar. Characteristics, treatment and outcome in heart failure with preserved vs. reduced ejection fraction: The Atherosclerosis Risk in Communities (ARIC) Study.

#1891: Deepak K. Gupta, Davide Castagno, Madoka Takeuchi, Amil M. Shah, Scott D. Solomon; Ervin Fox; Ken Butler; Tom Mosley. Phenotypic profile of heart failure with preserved ejection fraction in African Americans: risk factors, cardiac structure and function, and prognosis..

#2061: Umair Khalid, Anita Deswal, Biykem Bozkurt, Salim Virani, Vijay Nambi, Christie Ballantyne, Patty Chang, Laura Loehr, Wayne Rosamond, Sunil Agarwal. BNP as a prognostic marker in obese patients with acute decompensated heart failure and preserved ejection fraction.

#1942: Deepak K. Gupta, Amil M. Shah, Scott D. Solomon; Others welcome. Cardiac structure and function in elderly African-Americans with heart failure with preserved ejection fraction.

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/

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.

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