ARIC Manuscript Proposal #3245

PC Reviewed: 10/0918	**Status: _____**	**Priority: ____**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Systemic inflammation in mid- and late-life and late-life cardiac structure and function: The Atherosclerosis Risk in Communities study

b. Abbreviated Title (Length 26 characters): CRP and cardiac function

2. Writing Group:
Writing group members:
Aaron J. Cohen, Brian Claggett, Scott Solomon, Christie Ballantyne, Elizabeth Selvin, Amil M. Shah, OTHERS WELCOME

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

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3. Timeline:
September-November 2018: Data analysis
December 2018-January 2019: Drafting and submitting of manuscript

4. Rationale:

Over 5.8 million people in the United States suffer from heart failure (HF), which is associated with heightened morbidity and mortality, particularly among the elderly[1].

Impairments in cardiovascular structure and function underlie the development of clinical heart failure. Beyond conventional measures of left ventricular (LV) structure and function, such as LV ejection fraction (LVEF) and hypertrophy (LVH), measures of LV diastolic function and novel strain-based measures of systolic function are also predictive of incident HF[2]. HF with preserved LVEF (HFpEF) accounts for the majority of prevalent HF in the elderly, and is associated with a high prevalence of co-morbidities, such as obesity, chronic kidney disease, and diabetes mellitus, that have been linked to a pro-inflammatory state[3-4]. There is now speculation that co-morbidity-driven systemic inflammation may be a primary pathophysiologic driver of HFpEF development, with alterations in LV systolic and diastolic function resulting from resulting impairments in nitric oxide generation, reduced cyclic GMP, and altered titan phosphorylation[5]. While this hypothesis is supported by basic and translational data, there is little supportive human data to date. Previous studies have identified inflammatory biomarkers (e.g. hsCRP, IL-6) as predictors of incident HF, and of adverse outcomes among patients with prevalent HFrEF. Cross-sectional studies, generally among persons with established CVD, hypertension, or HF, demonstrate associations of circulating inflammatory biomarkers with impairments in both systolic and diastolic function[6-9]. However, limited community-based data are available relating markers of systemic inflammation to contemporary measures of the cardiac structure and function, particularly among the elderly who are at highest risk for HF development. There is also limited date regarding the impact of systemic inflammation in mid-life, and its change from mid- to late-life, on late-life cardiac structure and function. ARIC presents a unique opportunity to address these gaps in knowledge given the detailed clinical phenotyping of participants, longitudinal measurements of hs-CRP concentrations at three study visits spanning mid- to late-life (Visits 2,4,5), and detailed echocardiographic data in late life (Visit 5).

5. Main Hypothesis/Study Questions:

Main study question: To what extent do mid- and late-life hs-CRP concentrations relate to late-life measures of cardiac structure and function?

Main hypothesis: We hypothesize that higher concentrations of hs-CRP in both mid-life and late-life will associate with worse left ventricular diastolic and systolic function in late-life. Furthermore, we hypothesize that alterations in cardiac structure and function will partially account for the association of hs-CRP with risk of HF or death in late life.

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).

A. Cross-sectional analysis of the relationship between hsCRP and cardiac structure and function at Visit 5

Inclusion Criteria: ARIC Participants who attended visit 5
Exclusion Criteria: Participants with prevalent HF, CAD, and A-fib at visit 5.
Primary Exposure: hs-CRP concentrations measured at visit 5.
Primary Outcome(s): Cardiac structure and function at visit 5, defined with the following variables: Cardiac structure: LV mass, LV RWT; Systolic function: LVEF, GLS, GCS; Diastolic

function: LA volume index, e', E/e'. Will define diastolic dysfunction as having at least 2/4 abnormal measures of diastolic function.
Covariates: Demographics (i.e. age, race, sex); participant characteristics at Visit 5 that may predict cardiac dysfunction: BMI, lean body mass, fat free mass, prevalent DM, prevalent HTN, smoking, SBP, HR, GFR, NT-BNP (at visit 5), and hs-TNT (at visit 5)
Statistical Approach: Participants will be categorized based on quartiles of hs-CRP concentration at visit 5. Demographics and clinical characteristics at Visit 5 will be described by hs-CRP quartile group. P for trend across categories will be tested using linear or logistic regression as appropriate. Echocardographic measures will similarly be described by hs-CRP quartile group. We will assess the continuous relationship between hs-CRP concentrations and continuous measures of cardiac structure and function using multivariable linear regression. Hs-CRP concentrations will be log transformed to achieve a normal distribution. Multivariable models will adjust for participant demographics, and in a separate model will additionally adjust for clinical co-morbidities associated with hsCRP in unadjusted analyses. We will assess for possible non-linear relationships between log(hsCRP) and echocardiographic measures using restricted cubic splines.

B. Longitudinal analysis of the relationship between changes in hsCRP from Visit 2 to Visit 5 and echocardiography at Visit 5

Inclusion Criteria: ARIC participants who attended both visits 2 and 5
Exclusion Criteria: Participants with prevalent HF, CAD, and A-fib at either visit 2 or 5.
Primary Exposure: Change in hs-CRP from visit 2 to visit 5. If the absolute difference is not normally distributed, we will use the difference in log-transformed hs-CRP at Visits 2 and 5 as the primary exposure variable.
Primary Outcome(s): Cardiac structure and function at visit 5 as listed above.
Covariates: Demographics (i.e. age, race, sex); Clinical characteristics that may predict cardiac dysfunction as listed above, assessed at both Visit 2 and Visit 5.
Statistical Approach: Participants will be categorized by quartile of change in hs-CRP quartile from Visit 2 to Visit 5, and clinical and echocardiographic features will be described by these quartiles. Univariate and multivariable regression will be employed to determine the continuous relationship between change in hs-CRP and echocardiographic measures. Model 1 will adjust for age, sex, race, and hs-CRP concentration at Visit 2. Model 2 will additionally adjust for clinical covariates assessed at Visit 2 and associated with change in hsCRP in unadjusted analysis. Model 3 will additionally adjust for those covariates at Visit 5. In a secondary analysis, we will characterize change in hs-CRP as the individual slope of change calculated using values from Visits 2, 4, and 5.

C. Analysis of the extent to which echocardiographic measures account for the association of hs-CRP at Visit 5 with incident heart failure and death post-Visit 5

Inclusion Criteria: ARIC participants who attended visit 5 with data for echo and hsCRPs from that visit.
Exclusion Criteria: Participants with prevalent HF, CAD, and A-fib at visit 5.
Primary Exposure: hs-CRP concentration at visit 5
Mediating Exposure: Echocardiographic measures of cardiac structure and function associated with hsCRP concentrations in analyses A and B above.
Primary Outcome: Incident heart failure and death post-Visit 5

Covariates: Participant demongraphics and characteristics at Visit 5 that may predict both cardiac dysfunction and incident HF as described above.
Statistical Approach: We will use univariate and multivariable Cox proportional hazard models to determine the association of hsCRP with the composite of incident HF or death. If hsCRP is significantly associated with the outcome, we will determine the extent to which associated echocardiographic measures account for this association. This will accomplished by comparing the coefficients for hsCRP from models not including or including relevant echo measures as covariates. In an exploratory analysis, we will determine the association of hsCRP with inclident HFpEF and HFrEF.

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/mantrack/maintain/search/dtSearch.html

__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)?

1. MPF #1504: CRP, WBC, and Heart Failure Incidence; writing group: Folsom, Bekwelem, Lutsey, Loehr, Agarwal, Astor, Ballantyne
2. MPF #3001: The Impact of the Severity, Duration and Longitudinal Changes in the Metabolic Syndrome on the Risk of Incident Heart Failure; writing group: Tolulope Adesiyun, Lucia Kwak, Kavita Sharma, Vijay Nambi, Erin Michos, Ian Neeland, Roger Blumenthal, Christie Ballantyne, Elizabeth Selvin, Josef Coresh, Chiadi Ndumele
3. MPF #2207: Associations of C-reactive protein over six years with incident diabetes, cardiovascular events and mortality; writing group: Christina M. Parrinello; Pamela L. Lutsey; Christie M. Ballantyne; Aaron R. Folsom; Jim S. Pankow; Elizabeth Selvin

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 https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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:

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2. Shah, A., Claggett, B., Loehr, L., et al. Heart failure stages among older adults in the community. *Circulation.* 2017; 135: 224-240.
3. Ather, S., Chan, W., Bozurkt, B., et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. *J AM Coll Cardiol.* 2012; 59: 998-1005.
4. Shah SJ., Kitzman DW,. Borlaug BA., et al. Phenotype-specific treatment of heart failure with preserved ejection fraction: a multiorgan roadmap. *Circulation*. 2016; 134: 73–90.
5. Paulus, W.J. and Tschope, C. A Novel Paradigm for Heart Failure with Preserved Ejection Fraction. *JACC.* 2013; 62(4): 263-71.
6. Vasan, R.S., Sullivan, L., Roubenoff, R., et al. Inflammatory Markers and Risk of Heart Failure in Elderly Subjects Without Prior Myocardial Infarction. *Circulation*. 2003; 107: 1486-91.
7. Tang, W.H., Shrestha, K., Van Lente, F., et al. Usefulness of C-Reactive Protein and Left Ventricular Systolic Heart Failure. *Circulation.* 2008; 101: 370-73.
8. Kalogeropoulous, A., Georgiopoulou, V., Psaty, B.M., et al. Inflammatory Markers and Incident Heart Failure Risk in Older Adults: The Health, Aging, and Body Composition Study. *J Am Coll Cardiol.* 2010; 55(19): 2129-2137.

9. Shah, S.J., Marcus, G.M., Gerber, I.L., et al. High-Sensitivity C-Reactive Protein and Parameters of Left Ventricular Dysfunction. *Journal of Cardiac Failure.* 2006; 12(1): 61-65.