ARIC Manuscript Proposal #4206

PC Reviewed: 02/14/23 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Cardiac Structural and Functional Predictors of Fatigue in Heart Failure

b. Abbreviated Title (Length 26 characters): Predictors of Fatigue in Heart Failure

2. Writing Group:

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

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3. Timeline: Manuscript completed January 2023

4. Rationale:

Heart failure affects an estimated 6.2 million adults in the United States[1] with a projected increase of 46% by the year 2030. It causes significant morbidity and mortality with nearly 80,000 heart failure-related deaths reported in 2016.[1] Fatigue is one of the most frequently reported symptoms of heart failure[2] causing significant patient distress.[3,4] Despite guideline directed medical therapy, high symptom burden[5], mortality, and hospitalization as well as poor quality of life persist for both patients with heart failure with reduced (HFrEF) and preserved (HFpEF) ejection fraction. [6,7,8] **Fatigue is a prevalent, persisting, and distressing symptom for patients with heart failure.**

Fatigue in heart failure is divided into two, often co-occurring constructs that are important to the lived experience of heart failure patients: 1) generalized fatigue and 2) exertional fatigue. Exertional fatigue is directly related to exertion while general fatigue is a multi-dimensional, full-body experience not related to exertion. Evidence suggests that fatigue influences important clinical and patient reported outcomes such as quality of life[9,10], physical and emotional health[11], higher healthcare utilization[12,13,14], and increased hospital length of stay[14,15], mortality[16,17], and adverse cardiovascular events.[18] Therefore, understanding key predictors of both general and exertional fatigue in heart failure is critically important for improving patient reported and clinical outcomes.

There are key gaps in the literature relating to fatigue in heart failure: 1) current literature primarily focuses on individual biomarker correlates of only general fatigue and fails to examine other important indicators of cardiac structure and function that could influence fatigue symptoms and **2)** differences in fatigue between HFrEF and HFpEF have not yet been explored.

Echocardiographic assessment of cardiac structure and function correlates with some heart failure symptoms and provides prognostic information regarding prospective outcomes in patients with heart failure.[19,20,21] However, the relationship between echocardiographic parameters and fatigue symptoms in heart failure have not yet been examined. It is therefore unclear which, if any, echocardiographic measures are associated with the fatigue experience for heart failure patients. Understanding how key echocardiographic parameters in heart failure relate to fatigue can enhance our understanding of the physiologic underpinnings of the symptom experience for patients with heart failure.

The purpose of this study is to understand how echocardiographic measures of cardiac structure and function and heart failure phenotype relate to the presence or absence of different fatigue types in those with prevalent heart failure.

5. Main Hypothesis/Study Questions:

Determine whether among those with prevalent heart failure:

1. Type of echocardiographic abnormalities are associated with fatigue type
2. Severity of echocardiographic abnormalities are associated with fatigue type
3. Overall number of echocardiographic abnormalities are associated with fatigue type

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 study will be an analysis of visit 5 participants with a prior diagnosis of heart failure to determine the relationship between key echocardiographic parameters and fatigue type. Fatigue type was previously determined using latent class analysis in individuals with prevalent heart failure at Visit 5. Four fatigue classes were identified: 1) High General & High Exertional Fatigue, 2) High General & Low Exertional Fatigue, 3) Moderate General & Moderate Exertional Fatigue, and 4) Low/No Fatigue.

Exposures: The exposure will be echocardiographic parameters collected at visit #5. The parameters we will examine are detailed below in table 1. We will examine these variables as both dichotomous (abnormal or not abnormal) and categorized into tertiles (to evaluate severity of echocardiographic abnormalities).

Table 1. Echocardiographic parameters from ARIC Cohort Visit 5 for proposed analyses

Parameter	**Scale**	**Abnormal**	
Left Ventricular Structure		**Men**	**Women**
LV mass index	$g/m^{2.7}$	>96.1	>83
Left Ventricular (LV) Systolic Function			
LV Ejection fraction	%	<60	<59
Longitudinal Strain	% (adjusted for heart rate)	< -16%	< -16%
Circumferential Strain	% (adjusted for heart rate)	< -23%	< -23%
Left Ventricular (LV) Diastolic Function			
LA diameter	cm	>4.0	>3.7
LA volume index	ml/m^2	>31	>30
Lateral TDI e`	cm/s	<5.4	<5.1
Septal TDI e`	cm.s	<4.6	<4.5
Lateral E/e` ratio	ratio	>11.5	>13.3
Septal E/e` ratio	Ratio	>13.3	>15.1
Right Ventricular Function			
RV fractional area change; Tricuspid annular peak systolic myocardial velocity	cm/s	Threshold for dysfunction not defined in ARIC; continuous variable	
Pulmonary hypertension			
Estimated PASP	mmHg	>32	>32

Outcomes: The outcome will be an individual's fatigue type: 1) High General & High Exertional Fatigue, 2) High General & Low Exertional Fatigue, 3) Moderate General & Moderate Exertional Fatigue, and 4) Low/No Fatigue.

Inclusion criteria: Participation in visit 5 and have prevalent heart failure

Exclusion criteria: Missing data on fatigue measures and echocardiogram, and the small number of individuals that are non-black or non-white.

Covariates: We will adjust for age, race, sex, education level, smoking status, BMI, diabetes, systolic blood pressure, eGFR (creatinine and cystatin C), total cholesterol, HDL cholesterol, triglycerides, and the use of antihypertensives, beta-blockers, diuretics, psychotropics, or CNS depressants in the last 4 weeks.

Summary of Data Analysis:

- Exploratory data analysis will be performed. Continuous variables will be described using means and standard deviations or medians and IQR depending upon data distributions. Categorical or dichotomous variables will be described with percentages and frequency counts. Data will be evaluated for data distributions, skewedness, and missing data. Alpha will be set at 0.05 and all inference tests will be two-sided.
- We will compare echocardiographic parameters across fatigue classes (or factors or cross-categories) using independent t-test, chi squared test, and ANOVA for >2 group comparisons.
- We will perform multivariable multinomial latent class regression using the 3-step method for latent class regression:
    - Examine the association between different individual echocardiographic parameters and fatigue type among those with prevalent heart failure.
    - Examine whether a greater number of echocardiographic abnormalities (dichotomized as normal or abnormal) are associated with fatigue type
    - Examine whether the severity of echocardiographic abnormalities (categorized into tertiles) is associated with fatigue type
    - NOTE: we will use the 3-step method for latent class regression described by Asparouhov & Muthen[22] to account for classification error when assigning the most likely latent class to each individual participant.
- We will compare the distribution of fatigue classes between heart failure phenotype (HFrEF v HFpEF) using chi-squared tests
- We will perform multivariable multinomial latent class regression stratifying on heart failure phenotype to:
    - Examine whether associations between fatigue type and echo parameters vary as a function of heart failure phenotype

Sensitivity Analyses:

- We will perform sensitivity analyses:

    - excluding individuals with comorbid COPD or other respiratory conditions.
    - excluding those with a confirmed diagnosis of depression, and those with cancer receiving active treatment at visit 5.
    - Excluding those classified as frail.
    - Stratifying individuals on whether they had an ADHF hospitalization in the year prior to visit 5.
- prevhf52 (n=907) and prevdefposshf51 (n=1114) will be used as our primary definitions of prevalent heart failure diagnosis. However, we will perform a sensitivity analysis using prevdefhf51 (n=355) as our definition because it is the most specific definition.
- We will perform a sensitivity analysis using the clinical cut points for LVEF (Women <53%; Men <52%) rather than <60% or >60% as described above.
- These analyses may be limited by power due to the number of individuals who would need to be excluded.

Additional Secondary Analyses:

- We may consider additional analyses examining the relationship between echocardiographic parameters and fatigue type in those without heart failure.

Limitations:

- Risk of unidentified confounding.
- Over-representation of HFpEF in the visit 5 dataset due to earlier mortality of HFrEF cohort members.
- Exertional fatigue here is being operationalized using a scale that measures exertional dyspnea. We are conceptualizing exertional dyspnea as an indicator of the larger construct of exertional fatigue. It is possible that this operationalization does not capture individuals who experience exertional fatigue, but little to no dyspnea (exertion limited by angina, muscle weakness, etc.).

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes ___X_ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 current derived consent file ICTDER05 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)?

- ARIC Manuscript Proposal # 3674 - The Prognostic Role of ST2 in Heart Failure: Atherosclerosis Risk in Communities (ARIC) Study
- ARIC Manuscript Proposal # 1276 - Exhaustion and risk for congestive heart failure: The Atherosclerosis Risk in Communities (ARIC) Study

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 https://sites.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.

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