ARIC Manuscript Proposal #3899

PC Reviewed: 7/13/21 **Status: _____** **Priority: 2**
SC Reviewed: _________ **Status: _____** **Priority: ____**

1.a. Full Title: Association of Adiposity with Left Atrial Function: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): LA Function in Obesity

2. Writing Group:
Joseph J. Decker, Romil Parikh, Riccardo Inciardi, Michael Zhang, Chiadi Ndumele, Jeremy Van't Hof, Alvaro Alonso, Amil M. Shah, Scott D. Solomon, Lin Y. Chen, others welcome.

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

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3. Timeline:
Statistical analysis: 3 months
Manuscript preparation: 4 months

4. Rationale:

Atrial myopathy—characterized by abnormalities in left atrial (LA) structure and function—are linked to increased risk of AF, ischemic stroke, heart failure (both HFpEF and HFrEF), dementia, and CV death. [1-6] Importantly, the associations with increased risk of adverse CV and neurocognitive outcomes are often independent of AF. [7] Moreover, recent studies have shown that even before LA enlargement is manifest, lower LA function is associated with higher risk of adverse outcomes. [8] Despite the significant prognostic role of impaired LA function, our etiological understanding remains incomplete, particularly in relation to modifiable risk factors such as obesity.

Obesity is an independent risk factor for AF and HFpEF. [9-10] The proposed mechanisms include alterations in cardiovascular hemodynamics, which predispose to changes in both LA and left ventricular (LV) structure and function. Specifically, metabolically active adipose tissue stimulates increased cardiac output, which in combination with elevated peripheral resistance leads to LA dilation, eccentric LV hypertrophy, and modest effects on LV diastolic function with no significant impact on LV systolic function. [11-13] Obesity is traditionally defined by elevated body mass index (BMI); however, measures of central adiposity such as waist circumference (WC) and waist:hip ratio (WHR) are alternative measures of obesity, which have been suggested to be superior to BMI in predicting cardiovascular risk. [14-15]

While there is extensive literature on obesity as a risk factor for echocardiographic changes in LA structure, [16-18] there is a paucity of data on the relationship of adiposity measures to LA function. Limited studies have found impaired LA function in obese individuals, as measured by BMI and WC. [19-20] Increased pericardial adipose tissue has also been shown to be associated with impaired LA reservoir and conduit functions. [21] However, prior studies have not evaluated the association of longitudinal change in measures of adiposity over time with LA function. Additionally, it is unknown if the effects of adiposity on LA function are independent of LA size and LV size and function.

Therefore, we aim to assess the association of longitudinal change in adiposity measures with LA function, controlling for LV size and function.

5. Main Hypothesis/Study Questions:

Aim:
Evaluate the association of changes in measures of adiposity between Visits 4 and 5 with LA function on echocardiogram at Visit 5.

Hypothesis 1:
Compared with maintained optimal BMI between Visits 4 and 5, (1) maintained suboptimal BMI, (2) increasing BMI, will be associated with lower LA contractile, conduit and reservoir functions at Visit 5.

Hypothesis 2:
Compared with maintained optimal WC between Visits 4 and 5, (1) maintained suboptimal WC, (2) increasing WC, will be associated with lower LA contractile, conduit and reservoir functions at Visit 5.

Hypothesis 3:
Compared with maintained optimal WHR between Visits 4 and 5, (1) maintained suboptimal WHR, (2) increasing WHR, will be associated with lower LA contractile, conduit and reservoir functions at Visit 5.

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 population:
Inclusion: ARIC participants with LA function data at Visit 5.
Exclusion: Participants with missing BMI, waist circumference or hip circumference measurements at visits 4 or 5, those with prevalent AF or heart failure at Visit 5, those with underweight BMI (BMI <18.5) at visit 4 or 5, and those with missing covariate data at visit 5.

Exposure measurement:
Body mass index (BMI): BMI is calculated as weight in kilograms divided by height in meters squared and is measured at visits 4 and 5. Maintained optimal BMI will be defined as BMI <30 kg/m^2 between visits 4 and 5 and maintained suboptimal BMI will be defined as BMI ≥30 between visits 4 and 5. Additional categories will include increasing BMI and decreasing BMI.

Waist circumference (WC): WC is measured at visits 4 and 5. Maintained optimal WC will be defined as WC <102 cm (40 in) in men and <88 cm (35 in) in women between visits 4 and 5 and maintained suboptimal WC will be defined as WC ≥102 cm in men and ≥88 cm in women between visits 4 and 5. Additional categories will include increasing WC and decreasing WC.

Waist:hip ratio (WHR): Waist and hip circumferences are measured at Visits 4 and 5. Maintained optimal WHR will be defined as WHR <0.8 and 0.9 in women and men respectively between visits 4 and 5. Maintained suboptimal WHR will be defined as WHR ≥0.8 and 0.9 in women and men respectively between visits 4 and 5. Additional categories will include increasing WHR and decreasing WHR.

Outcome measurement:
2D echocardiographic LA function variables measured at Visit 5 including LA reservoir, conduit and contractile function (all variables will be assessed continuously).

Covariates of interest (measured at Visit 5):
- Demographic variables: age, sex and race-field center
- Cardiovascular risk factors: systolic blood pressure (SBP), hypertension medications, diabetes (DM), smoking status (current, former, never), alcohol intake, triglycerides (TG), high density lipoprotein (HDL) cholesterol and physical activity.
- Clinical conditions: coronary heart disease (CHD), stroke and cancer
- Echocardiographic variables: left atrial volume index (LAVi), LV end diastolic volume (LVEDV), LV mass, LV relative wall thickness (RWT), LV longitudinal strain (LVLS), E/e’

Statistical analysis:

- Participant characteristics will be described using mean ± standard deviation for continuous variables, median (interquartile range) for highly skewed variables, and proportions for categorical variables, stratified by BMI categories obese (BMI ≥30) and non-obese (BMI <30).

- Multivariable linear regression will be used to evaluate the relationship between adiposity measures and LA function.

- Adiposity measures will be presented as the following groups:
  1. Maintained optimal adiposity measure
  2. Maintained suboptimal adiposity measure
  3. Increasing adiposity measure
  4. Decreasing adiposity measure

- LA function variables will be presented as adjusted means ± standard error.
- We will fit the following multivariable regression models:
  - Model 1: Adjusted for age, sex, race/field center, education
  - Model 2: Model 1 + SBP, DBP, hypertension medications, DM, CHD, stroke, smoking, alcohol intake, TG and HDL
  - Model 3: Model 2 + physical activity trajectory
  - Model 4: Model 2 + LAVi, LVEDV, LV mass, RWT, LVLS, E/e’

Additionally, we will perform a sensitivity analysis excluding participants with cancer.

Limitations:
Visits 4 and 5 are separated by approximately 15 years and as such there is the potential for selection bias resulting from loss to follow-up over this prolonged time period. Additionally, despite adjusting for multiple confounders, residual confounding may be present.

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)?**
Bello NA, Cheng S, Claggett B, Shah AM, Ndumele CE, Roca GQ, Santos AB, Gupta D, Vardeny O, Aguilar D, Folsom AR, Butler KR, Kitzman DW, Coresh J, Solomon SD. Association of Weight and Body Composition on Cardiac Structure and Function in the ARIC Study (Atherosclerosis Risk in Communities). Circ Heart Fail. 2016 Aug;9(8):e002978. doi: 10.1161/CIRCHEARTFAILURE.115.002978. PMID: 27512104; PMCID: PMC5218510.

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

___ A. primarily the result of an ancillary study (list number* __2015.29 (Chen) _)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________ __________ _________)

References:

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