ARIC Manuscript Proposal Form

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ARIC Manuscript Proposal Number: **# 4477**

1.a. Full Title: Association of pulmonary vascular remodeling with left ventricular structure and function, pulmonary pressure, and right ventricular dysfunction in late life.

b. Abbreviated Title (Length 26 characters): PV remodeling and echo

2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:
Writing group members:Aditya Dewanjee, Victoria Lamberson, Yimin Yang, Raul San Jose Estepar, George Washko, Kunihiro Matsushita, Michael Blaha, Brian Claggett, Amil M Shah, OTHERS WELCOME

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (The ARIC author should be involved enough in ARIC to be able to point the lead author to appropriate ancillary study PIs and to be able to search ARIC manuscript proposals if the lead author doesn't have the access needed to do such a search).

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3. Timeline:Data analysis will start once the proposal is approved. We anticipate the manuscript will be prepared within the next 6 months.

4. Rationale: The relationship between pulmonary vascular (PV) disease and cardiovascular disease (CVD) has long been recognized. Known cardiovascular risk factors are associated with pulmonary hypertension (PH), including diabetes[1], systemic hypertension[2], obesity[3], CKD[4], smoking[5], and atrial fibrillation[6]. Furthermore, the most common cause of PH is left-heart disease (LHD), otherwise referred to as WHO Group 2 Pulmonary Hypertension or PH-LHD. PH-LHD can be further categorized into isolated post-capillary PH (Ipc-PH) and combined pre- and post-capillary PH (Cpc-PH). Ipc-PH is characterized by passive pulmonary venous congestion with elevation of pulmonary pressure as a result of elevated left atrial pressure. In contrast, the elevation of pulmonary pressures seen in Cpc-PH exceed that which can be solely attributed to backward transmission of left atrial pressure and results from concomitant intrinsic pulmonary vascular disease. The presence of Cpc-PH is a poor prognostic indicator for PH-LHD [7, 8].

Histologic studies have identified specific morphologic changes that occur in the pulmonary vasculature in association with cardiac disease and heart failure, including increased pulmonary artery medial wall thickness and decreased luminal diameter associated [9-11]. However, there have been relatively few studies investigating how specific cardiovascular risk factors impact and modify the relationship between heart failure and pulmonary vascular remodeling [12, 13]. There is even less data to inform us on how specific markers of cardiac function, including LV hypertrophy, LV systolic function, LV diastolic function, RV systolic function, and RV filling pressures correlate with pulmonary vascular remodeling.

Having a greater understanding of pulmonary vascular remodeling that occurs in LHD and in conjunction with cardiovascular risk factors is of clinical interest. Pulmonary arterial hypertension, or WHO Group 1 PH, treatment modalities like Activin IIA receptor ligand inhibitors (Sotatercept), endothelin receptor antagonists, phosphodiesterase inhibitors, and prostacyclin analogues may have benefit in the subset of LHD patients with combined pre- and post-capillary PH. In fact, animal studies have shown that both Sotatercept and Sildenafil decreased pulmonary vascular remodeling in mice and rats with heart failure [14, 15].

A non-invasive method of measuring pulmonary vascular remodeling has been developed using non-contrast CT scans [16]. This modality measures the pulmonary small-vessel fraction, or percent of total pulmonary vascular luminal area that is made up of small vessels, with the most common threshold being below 5mm in diameter. CT-based PV pruning has been shown to correlate with pulmonary vascular remodeling on histology [17] and has been studied in multiple pulmonary disease states. These include COPD[18], bronchiectasis[19], asthma[20], CTEPH[21], acute PE[22], and PAH [23]. Notably, CT-based pruning in these studies has been found to correlate with greater RV size on CT[18], greater pulmonary vascular resistance and decreased cardiac index on RHC[21], RV functional metrics on CMR[24], and greater all-cause

mortality in patients without pulmonary disease [25]. However, little data exist regarding the relationship of clinical (HF) and subclinical left ventricular dysfunction on pulmonary vascular pruning.

In this analysis, we will characterize the patterns of pulmonary vascular remodeling, using CT-based measures of distal and pre-acinar pulmonary vascular volume, among older adults in the community. The novelty of this analysis lies in the fact that CT-based pulmonary vascular pruning and/or remodeling has not been studied in an older population with a high prevalence of cardiovascular risk factors and disease, nor have predictors and consequences of pulmonary vascular pruning in this population been described. Specifically, we will determine the association of cardiovascular risk factors, subclinical alterations in left ventricular structure and function, and clinical heart failure with PV remodeling in this population. Finally, we will relate PV pruning on CT to measures of pulmonary pressure, RV size and function, participant-reported dyspnea, functional capacity based on 2 minute walk, and risk of incident HF hospitalization.

5. Main Hypothesis/Study Aims:

1. Cardiovascular risk factors, such as hypertension, coronary artery disease, atrial fibrillation, obesity, smoking, and diabetes mellitus, will be associated with smaller distal pulmonary vascular area (i.e. greater pulmonary vascular pruning) as measured on CT.
2. Echocardiographic markers of worse LV systolic and diastolic function and filling pressure will be associated with smaller distal pulmonary vascular area.
3. Greater pulmonary vascular pruning will be associated with greater pulmonary artery pressure, greater RV enlargement, and worse RV function.
4. Greater pulmonary vascular pruning will be associated worse functional capacity and clinical outcomes (incident HF, mortality).

6. Design and analysis - please address the following aspects:

a) inclusion/exclusion

a. Inclusion
   i. Attended seventh study visit
   ii. Underwent noncontrast inspiratory CT at or near time of the seventh visit with measurable metrics of pulmonary vascular remodeling performed by the Applied Chest Imaging Laboratory (BWH)

b) study design

a. In this analysis we will evaluate the relationship between computed tomography measures of distal pulmonary vascular morphology, or pulmonary vascular pruning, with cardiovascular risk factors, echocardiographic measures of LV structure, function and filling pressure, and RV function, self-reported dyspnea, functional capacity based on 2-minute walk distance (2MWD), risk of incident HF, and HF stages. Finally, among participants with prevalent HF, we will assess the associations of pulmonary vascular pruning with all-cause mortality.

c) outcome and other variables of interest with specific reference to the time of their collection

a. Analysis 1: Describe association between cardiovascular risk factors with vascular remodeling parameters.

i. Exposure: Presence of cardiovascular risk factors. Risk factors will include hypertension, coronary artery disease, chronic kidney disease, atrial fibrillation, obesity, smoking status, and diabetes mellitus
    1. Hypertension: defined from self-report, medication use, or blood pressure ≥ 140/90 mm Hg at visits 5 and 7.
    2. Coronary artery disease: based on ARIC surveillance for CHD events including definite or probable MI and coronary revascularization at any point before seventh visit
    3. Chronic Kidney Disease: defined as estimated glomerular filtration rate of <60 mL/min/1.73 m2, calculated using the Chronic Kidney Disease Epidemiology Collaboration equation
    4. Atrial Fibrillation: ascertained based on hospital discharge ICD codes and ECGs at study visits
    5. Obesity: Defined as BMI >= 30, with BMI calculated by dividing measured weight (in kilgorams) by height (in meters) squared as measured at the seventh visit
    6. Smoking status: Ascertained by an interviewer-administered questionnaire, and categorized as never smokers, former smokers, and current smokers
    7. Diabetes mellitus: self-report of diagnosis by a physician, medication use, fasting glucose >126 mg/dL, or nonfasting glucose >200 mg/dL at visits 5 and 7

ii. Outcomes:
    1. Measurements of distal vascular volume for pulmonary arteries and veins defined as vessels less than 5 mm^2
        a. $BV5_{arterial}$: Area of pulmonary arterial vessels with diameter less than 5mm
        b. $BV5_{venous}$: Area of pulmonary venous vessels with diameter less than 5mm
        c. $BV5_{arterial}$/TBV: Fraction of total pulmonary vessel area made up of arterial vessels with diameter less than 5mm
        d. $BV5_{venous}$/TBV: Fraction of total pulmonary vessel area made up of venous vessels with diameter less than 5mm
        e. $BV5_{total}$/TBV: Fraction of total pulmonary vessel area made up of vessels, both arterial and venous, with diameter less than 5mm
    2. Measurements of proximal vascular volume for pulmonary arteries and veins defined as vessels greater than 10 mm^2 (
        a. $BV10_{arterial}$: Area of pulmonary arterial vessels with diameter greater than 10mm
        b. $BV10_{venous}$: Area of pulmonary venous vessels with diameter greater than 10mm
        c. $BV10_{arterial}$/TBV: Fraction of total pulmonary vessel area made up of arterial vessels with diameter greater than 10mm

d. $BV10_{venous}$/TBV: Fraction of total pulmonary vessel area made up of venous vessels with diameter greater than 10mm)

3. All these metrics will be calculated using noncontrast cardiac CT scans collected at or near time of the seventh visit

iii. Covariates: Age, sex, ARIC study site, self-reported race

b. Analysis 2: Describe associations of pulmonary vascular remodeling measures with left-heart echocardiographic markers

i. Exposures:

1. LV structure markers: LVEDV, LVMi, mean LV wall thickness
2. Systolic function markers: LVEF, Longitudinal Strain, Circumferential Strain
3. Diastolic function markers: E/A ratio, E/E' ratio, E'
4. LA structure markers: LA area, LA volume index, LA strain
5. Outcomes:

a. $BV5_{arterial,}$ $BV5_{venous}$,$BV5_{arterial}$/TBV, $BV5_{venous}$/TBV, $BV5_{total}$/TBV, $BV10_{arterial}$, $BV10_{venous,}$ $BV10_{arterial}$/TBV, $BV10_{venous}$/TBV

ii. Covariates:

1. Minimally adjusted model: Age, sex, ARIC study site, self-reported race
2. Adjusted model A: Age, sex, ARIC study site, self-reported race, hypertension, coronary artery disease, chronic kidney disease, atrial fibrillation, obesity, smoking status, and diabetes mellitus
3. Adjusted model B will include the above as well as:

a. Low Attenuation Area % (LAA%): Defined as percentage of total lung volume that was less than -950 Hounsfield units

b. High Attenuation Area (HAA%): Defined as percentage of total lung volume that was less than -250 Hounsfield units but greater than -600 Hounsfield units

c. Analysis 3: Describe associations of pulmonary vascular remodeling measures with right-heart echocardiographic markers

i. Exposures:

1. $BV5_{arterial,}$ $BV5_{venous}$,$BV5_{arterial}$/TBV, $BV5_{venous}$/TBV, $BV5_{total}$/TBV, $BV10_{arterial}$, $BV10_{venous,}$ $BV10_{arterial}$/TBV, $BV10_{venous}$/TBV

ii. Outcomes: TR velocity, RV fractional area change, TAPSE, Tricuspid annular S'

iii. Covariates: Minimally adjusted model and fully adjusted model as described above

d. Analysis 4: Describe association between vascular remodeling measures and functional metrics (self-reported dyspnea, 2MWD, incident cardiac events, and death

i. Exposures:

1. $BV5_{arterial,}$ $BV5_{venous}$,$BV5_{arterial}$/TBV, $BV5_{venous}$/TBV, $BV5_{total}$/TBV, $BV10_{arterial}$, $BV10_{venous,}$ $BV10_{arterial}$/TBV, $BV10_{venous}$/TBV

ii. Outcomes:
1. Self-reported dyspnea score
2. 2-minute walking distance
3. Incident cardiovascular events
4. Incident heart failure
5. Death

iii. Covariates: Minimally adjusted model and fully adjusted model as described above

e. Analysis 5: Describe pulmonary vascular remodeling parameters in cohort overall, stratified by prevalent HFrEF, prevalent HFpEF, and no prevalent heart failure

i. Exposures:
1. ACC/AHA Heart Failure Stage defined as below based on Visit 5 and 7 data:

Table 1. Definition of ACC/AHA Heart Failure Stages and Classification Criteria Used in This Study

HF Stage	ACC/AHA Guideline Definition	Operational Definition in This Analysis
Stage 0	Not meeting criteria for HF Stages A, B, C, or D	None of the following clinical risk factors: prevalent cardiovascular disease (coronary artery disease, stroke, or peripheral arterial disease), hypertension, diabetes mellitus, obesity, metabolic syndrome, or chronic kidney diseaseNone of the following cardiac structural or functional abnormalities: Abnormal LVEF, regional wall motion abnormality, LV enlargement based on LVEDV indexed to BSA, left ventricular hypertrophy based on LV mass indexed to height$^{2.7}$, moderate or greater aortic stenosis, aortic regurgitation, mitral regurgitation, or mitral stenosis
Stage A	At high risk for HF but without structural heart disease or symptoms of HF	At least 1 of the following clinical risk factors: prevalent cardiovascular disease (coronary artery disease, stroke, or peripheral arterial disease), hypertension, diabetes mellitus, obesity, metabolic syndrome, or chronic kidney diseaseNone of the following cardiac structural or functional abnormalities: Abnormal LVEF, regional wall motion abnormality, LV enlargement based on LVEDV indexed to BSA, left ventricular hypertrophy based on LV mass indexed to height$^{2.7}$, moderate or greater aortic stenosis, aortic regurgitation, mitral regurgitation, or mitral stenosis
Stage B	Structural heart disease but without signs or symptoms of HF	At least 1 of the following cardiac structural or functional abnormalities: abnormal LVEF, regional wall motion abnormality, LV enlargement based on LVEDV indexed to BSA, left ventricular hypertrophy based on LV mass indexed to height$^{2.7}$, moderate or greater aortic stenosis, aortic regurgitation, mitral regurgitation, or mitral stenosis
Stage C1	Structural heart disease with earlier or current symptoms of HF	Prevalent HF not identified through a previous hospitalization and instead based on self-report of HF or treatment for HF with at least 1 of the following: (1) subsequent confirmation of self-report by treating physician or the participant, or (2) an NT-proBNP at ARIC visit 4 or 5 of ≥125 pg/mL
Stage C2		Prevalent HF identified through a previous hospitalization based on (1) committee adjudicated HF hospitalization since 2005,[13] or (2) hospitalization with an ICD code 428 before 2005[8]
Stage D*	Refractory HF requiring specialized interventions	Left ventricular assist device or chronic inotropic therapy

[26]

2. For those patients with Stage C-D heart failure, stratify patients based on HFrEF (documented LVEF <50%) or HFpEF (no documented LVEF <50%)

ii. Outcomes:
1. $BV5_{arterial,}$ $BV5_{venous}$,$BV5_{arterial}$/TBV, $BV5_{venous}$/TBV, $BV5_{total}$/TBV, $BV10_{arterial}$, $BV10_{venous,}$ $BV10_{arterial}$/TBV, $BV10_{venous}$/TBV

iii. Covariates: Minimally adjusted model and fully adjusted model as described above

d) summary of data analysis

a. Summary statistics of primary outcomes presented as means and SD
b. We will compare all continuous variables using both multivariable linear regression and restricted cubic splines using the covariates as listed above

c. In analysis 5, we will stratify patients by HF stage, test for trend across all HF stages, and perform pairwise comparisons between individual HF stages using multivariable linear regression with covariates as defined above.
d. We will compare pulmonary vascular metrics (Arterial BV5/TBV, Venous BV5/TBV, Total BV5/TBV, Arterial BV10/TBV, Venous BV10/TBV, and Total BV10/TBV) between patients with HFrEF and HFpEF using multivariable linear regression
e. We will use multivariable Cox proportional hazard models and restricted cubic splines to
    i. describe the association with incident HF among HF-free study participants
    ii. describe association with mortality in all patients with prevalent heart failure, and then stratified by HFrEF (documented LVEF < 50%) or HFpEF (no documented LVEF < 50%)
f. Sensitivity Analysis
    i. Exclude patients with significant COPD based on Spirometry at Visit 5
    ii. Exclude patients with known severe Asthma, PAH, CTEPH, Bronchiectasis

e) Any anticipated methodologic limitations or challenges if present

1. Cross-sectional study design at Visit 7 with limit causal inference
2. CT data is only available in a subset of ARIC participants at Visit 7 without a history of CAD, which may limit severity of cardiovascular disease in this cohort, and may limit the generalizability of the study findings
3. Limited number of incident events post-Visit 7 will limit power for these analyses
4. Significant missing data for tricuspid regurgitation spectral Doppler-based PASP assessment may further limit power for analyses relating pulmonary vascular remodeling measures to pulmonary pressure.

f) Will the author need Limited data to complete the proposed manuscript? ☐ Yes, Limited data is needed (Provide a brief (2-3 sentences) justification for requesting PHI data) . ☒ No, De-identified data will be sufficient.

*Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic, Geocoded, Proteomics/Somalogic, and other -omic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? (Non-ARIC analysis means that the authors are not regarded as ARIC investigators and the "ARIC author" is essentially just a facilitator rather than an integral part of the writing group.) ☐ Yes ☒ 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 is distributed to ARIC PIs annually, 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 ☒ 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 or the "sponsoring" ARIC 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 website at: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website□Publications□Proposal Search]

☒ 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)?
None found

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use current [or ongoing] ancillary study data (this includes ACHIEVE)? ☒ Yes ☐ No → Skip to question 12

11.b. If yes to 11.a., is the proposal

☒ A. primarily the result of an ancillary study

☐ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables)

11.c. If yes to 11.a., list number* 2016.23__

*ancillary studies are listed by number
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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**

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