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Associations between atrial cardiopathy and cerebral amyloid: The ARIC-PET study

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BRIEF COMMUNICATION

Associations Between Atrial Cardiopathy and Cerebral Amyloid: The ARIC-PET Study

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BACKGROUND: Atrial fibrillation (AF) is a risk factor for cognitive decline, possibly from silent brain infarction. Left atrial changes in structure or function (atrial cardiopathy) can lead to AF but may impact cognition independently. It is unknown if AF or atrial cardiopathy also acts on Alzheimer disease–specific mechanisms, such as deposition of β-amyloid.

METHODS AND RESULTS: A total of 316 dementia-free participants from the ARIC (Atherosclerosis Risk in Communities) study underwent florbetapir positron emission tomography, electrocardiography, and 2-dimensional echocardiography. Atrial cardiopathy was defined as ≥1: (1) left atrial volume index >34 mL/m^2; (2) P-wave terminal force >5000 μV×ms; and (3) serum NT-proBNP (N-terminal pro-B-type natriuretic peptide) >250 pg/mL. Cross-sectional associations between global cortical β-amyloid (>1.2 standardized uptake value ratio) and adjudicated history of AF and atrial cardiopathy, each, were evaluated using multivariable logistic regression. Participants (mean age, 76 years) were 56% women and 42% Black individuals. Odds of elevated florbetapir standardized uptake value ratio were significantly increased among those with atrial cardiopathy (odds ratio, 1.81; 95% CI, 1.02–3.22) and doubled for those with enlarged left atrial volume index after adjustment for demographics/risk factors (95% CI, 1.04–4.61). There was no association between P-wave terminal force or NT-proBNP and elevated florbetapir standardized uptake value ratio, nor between AF and elevated standardized uptake value ratio.

CONCLUSIONS: Among healthy, nondemented community-dwelling older individuals, we report an association between atrial cardiopathy, left atrial volume index, and elevated brain amyloid, by positron emission tomography, without a similar association in individuals with AF. Potential limitations include reverse causation and survival bias. Ongoing work will help determine if changes in cardiac structure and function precede or occur simultaneously with amyloid deposition.

Key Words: atrial cardiopathy ■ cognitive decline ■ cohort study ■ positron emission tomography

Poststroke cognitive decline and dementia represent a significant public health problem.[1,2] There have been several reasons postulated as the cause of poststroke cognitive decline, but the precise mechanisms remain unclear. Patients with cardioembolic stroke in particular are at increased risk for cognitive decline compared with other stroke subtypes.[3] Atrial fibrillation (AF), the most common cause of cardioembolic stroke, has been suggested as the potential driver in this association. However, growing literature suggests that the paradigm of AF as the only pathway leading to cardioembolic stroke is not sufficient, with patients with implantable cardiac devices, for example, sometimes showing no relationship between the timing of AF and the stroke event.[4,5] A newer model now suggests AF is only one mechanism by which embolization from the left atrium (LA) can occur.[6] A state of atrial cardiopathy, or dysfunction of the LA, has been defined in different ways, but the overarching goal is to capture the potentially causative, pathophysiologic changes that lead to thromboembolism. The ARCADIA (Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke) trial is one example of an ongoing secondary stroke prevention trial that uses a biomarker-driven approach to define LA dysfunction, randomizing patients to different

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medications (antiplatelet versus anticoagulation) based on the presence of atrial cardiopathy.[7] We have previously demonstrated that subclinical changes in left ventricle structure and function were associated with increased brain β-amyloid deposition.[8] The aim of this study is to determine if the presence of atrial cardiopathy, defined using a definition similar to ARCADIA trial, was associated with the presence of aggregated brain β-amyloid in a cohort of older adults without dementia, independent of underlying vascular risk.

METHODS

The study was approved by the Institutional Review Board at all institutions involved, and informed consent was obtained. Data that support the findings of this study are available per ARIC (Atherosclerosis Risk in Communities) study policies.

The ARIC study is a community-based cohort study whose methods have been described in detail elsewhere.[9] In addition to the parent ARIC study, the ARIC Neurocognitive study enrolled patients for detailed cognitive assessments and magnetic resonance imaging, of whom 346 nondemented individuals were recruited to undergo florbetapir positron emission tomography (PET) (amyloid) imaging, in the ARIC-PET ancillary study.[10] Participants also had transthoracic echocardiography, cardiac monitoring, and venipuncture, as has been previously described.[11] The cardiac assessment occurred before, but <1 year, from PET. Individuals in the ARIC-PET study who were missing exposure data or covariates were excluded from this analysis (Figure).

Atrial Cardiopathy

Atrial cardiopathy for this study was defined using 3 different biomarkers, capturing different aspects of LA function. It required ≥1 of the following: P-wave terminal force >5000 μV×ms in ECG lead V1, serum amino terminal NT-proBNP (N-terminal pro-B-type natriuretic peptide) >250 pg/mL, and LA volume index (LAVI) ≥34 mL/m^2, per established guidelines.[12] P-wave terminal force was calculated by multiplying amplitude by duration from participant ECG. LAVI was specifically chosen instead of more frequently reported LA diameter (criteria used for ARCADIA trial), as data support this measure as superior for LA remodeling.[13] Participants were not required to have AF to meet criteria for atrial cardiopathy.

Brain Imaging

Florbetapir PET was conducted at the 3 enrolling sites with standardization performed to ensure effectively equivalent spatial resolution of 8.30 mm for the 3 sites. Radioisotope (florbetapir) was administered with a butterfly needle for the 20-minute (4×5 minutes) uptake scan, with image acquisition between 50 and 70 minutes. The Johns Hopkins University Department of Radiology, Section of High-Resolution Brain PET imaging core, reviewed all scans for image quality and conducted measurements of standardized uptake value ratios (SUVRs), as has been previously reported. The primary unit for analysis was a weighted average of 9 brain regions (orbitofrontal, prefrontal, superior frontal cortices, lateral temporal, parietal and occipital lobes, precuneus, and anterior and posterior cingulates), which were used to define a global cortical measure of aggregated β-amyloid. Elevated florbetapir was defined as SUVR >1.2, the sample median, because of the highly skewed distribution of the data.

Covariate Assessment

Covariates were defined on the basis of participant status at the time of the fifth study visit, with the exception of race, sex, and education level, which were defined at ARIC study baseline. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or antihypertensive medication use. Diabetes mellitus was defined as a hemoglobin A1C ≥6.5%. Low-density lipoprotein was analyzed continuously (mg/dL), as was body mass index (kg/m^2) and estimated glomerular filtration rate (mL/min per 1.73 m^2). Race was self-reported (Black or White race), as were smoking status and level of educational attainment. Smoking status was considered a binary variable, either having ever smoked cigarettes (ever smoker) versus never smoking. The 3 potential responses for education level were less than high school, graduation from high school or general educational development equivalent, or education beyond high school (college or graduate work). Coronary heart disease was defined as prevalent before visit 5 and was a binary variable. Prevalent AF was considered to be present if AF was diagnosed at any ARIC study visit preceding and including visit 5, concurrent with brain magnetic resonance imaging. AF diagnosis was based on the following criteria: standard ECG or presence of *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*, code 427.3x in the absence of open heart surgery in any prior hospitalization. Apolipoprotein E (APOE) alleles were considered for participants who gave consent for genetic data use, with alleles collapsed into a binary variable for the presence or absence of at least one APOE e4 allele.

Statistical Analysis

For continuous variables, means and SDs are reported; and for categorical variables, frequencies are reported. Multivariable logistic regression modeled the association of cerebral amyloid (SUVR >1.2),

with (1) each LA variable, (2) atrial cardiopathy, and (3) prevalent AF, separately, adjusted for confounders in stepwise models, with interaction terms for sex and race when appropriate. Model 1 adjusts for age, race, sex, education level, hypertension, diabetes mellitus, low-density lipoprotein, smoking history, body mass index, coronary heart disease, and estimated glomerular filtration rate. Model 2 adjusts for model 1 and prevalent AF. Model 3 adjusts for model 2, APOE e4 allele, and mild cognitive impairment (MCI). AF was excluded from the adjustment model when it was considered as an independent variable. Sensitivity analyses assessed for effect measure modification by APOE e4 allele and cognitive status, rather than adjusting for them as covariates. Covariates were chosen on the basis of associations in the literature, and were believed to potentially confound the relationship between LA function and cerebral amyloid.

RESULTS

A total of 316 participants met inclusion criteria (311 permitted APOE e4 use) and were aged 70 to 82 years, 56% were women, and 42% were Black individuals. Seventeen participants had prevalent AF, 98 met criteria for atrial cardiopathy, and 88 had MCI (Table 1). Demographics were also stratified by cognitive status, with no statistically significant differences between those with MCI and those cognitively normal (Table S1). Black participants were more likely to be hypertensive and have higher body mass index, low-density lipoprotein, and estimated glomerular filtration rate than White participants (details not shown).[10]

There was approximately 2 times the odds of elevated florbetapir SUVR among those participants with an LAVI ≥34 mL/m^2, with the effect estimate becoming larger and statistically significant after adjustment for AF, APOE e4, and MCI (95% CI, 1.04–4.61; model 3; Table 2), but no association was found among participants with an elevated P-wave terminal force (N=21) or elevated serum NT-proBNP (N=61). Prevalent AF (N=17), as an independent variable, was not associated with florbetapir SUVR >1.2. Among those with atrial cardiopathy, there were increased odds of florbetapir SUVR >1.2 in the more fully adjusted model, including APOE e4 and MCI (odds ratio [OR], 1.81; 95% CI, 1.02–3.22; model 3). There was no evidence of effect measure modification by APOE e4 (e4 allele OR, 1.43; no e4 allele OR, 2.03; *P*-interaction=0.81), race (*P*-interaction=0.86), or sex (*P*-interaction=0.52) when considering the relationship between atrial cardiopathy and elevated florbetapir SUVR (details not shown). Relationships between cardiac markers and amyloid were similar in the cognitively normal and MCI groups, without evidence of effect modification by cognitive status, although with loss of power because of smaller numbers (Table S2).

Table 1. Participant Demographics (N=316)

Characteristic	Value
Age, mean (SD), y	76 (5)
Women	177 (56)
Black race	135 (42)
History of ever smoking	182 (58)
Hypertension	233 (74)
Low-density lipoprotein, mean (SD), mg/dL	106 (33)
Diabetes mellitus	108 (34)
Body mass index, mean (SD), kg/m^2	29 (5)
Prevalent coronary heart disease	25 (8)
Estimated glomerular filtration rate, mean (SD), mL/min per 1.73 m^2	71 (17)
Education level	
Less than high school	51 (16)
High school graduate or equivalent	135 (43)
More than high school	130 (41)
Prevalent atrial fibrillation	17 (5)
APOE e4	98 (32)
Mild cognitive impairment	88 (27)

Values are number (percentage) unless otherwise specified; hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or antihypertensive medication use; diabetes mellitus was defined as a hemoglobin A1C ≥6.5%. APOE indicates apolipoprotein E.

DISCUSSION

In this cross-sectional analysis of a cohort of healthy, nondemented community-dwelling older individuals, we report a significant association between (1) LAVI and (2) atrial cardiopathy, defined using 3 different aspects of LA function, similarly to an ongoing clinical trial, and elevated PET florbetapir SUVR, an imaging marker for amyloid, when accounting for APOE e4 carriage and cognitive status. We recognize that there are limitations to this analysis. Cases of AF may have been missed, as diagnosis was based on in-clinic ECG data or adjudicated events from hospitalizations only. There is the possibility for reverse causation (because of the cross-sectional nature of the study) and survival bias. Although our results were robust to adjustment for potential confounders, we acknowledge the potential for unmeasured confounding. However, this work is novel in that our findings raise the possibility that cardiac disease in the form of a state of atrial cardiopathy, and the cellular pathological features that underlie it, may (directly or indirectly) impair brain integrity. This may lead to later life cognitive impairment through a brain

Table 2. Odds of Elevated Global Cortical Cerebral Amyloid by Florbetapir PET (SUVR >1.2) by Cardiac Variable (N=316)

Cardiac Independent Variable	No. With Specified Cardiac Variable	Model 1		Model 2		Model 3	
		OR	95% CI	OR	95% CI	OR	95% CI
LAVI ≥34 mL/m^2	50	1.87	0.93–3.58	2.11	1.03–4.31	2.18	1.04–4.61
P-wave terminal force >5000 μV×ms	21	0.85	0.33–2.19	0.88	0.34–2.29	0.79	0.29–2.14
Serum NT-proBNP >250 pg/mL	61	1.65	0.86–3.16	1.83	0.93–3.61	2.00	0.97–4.12
Atrial cardiopathy	98	1.55	0.92–2.62	1.70	0.98–2.92	1.81	1.02–3.22
Prevalent atrial fibrillation	17	0.65	0.23–1.87	N/A	N/A	0.73	0.24–2.17

Adjustment models: model 1=age, race (Black or White race), sex, education level (less than high school, high school graduation/equivalent, or more than high school), hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or antihypertensive medication use), diabetes mellitus (hemoglobin A1C ≥6.5%), low-density lipoprotein (mg/dL), smoking history (ever vs never), body mass index (kg/m^2), prevalent coronary heart disease, and estimated glomerular filtration rate (mL/min per 1.73 m^2). Model 2=model 1+prevalent atrial fibrillation. Model 3=model 2+apolipoprotein e4 and mild cognitive impairment (311 permitted apolipoprotein e4 use, so smaller sample). LAVI indicates left atrial volume index; N/A, nonapplicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio; PET, positron emission tomography; and SUVR, standardized uptake value ratio.

β-amyloidogenic mechanism in addition to, or even as a consequence of, cardioembolism and subsequent brain infarction.

LA enlargement, measured in our study using LAVI, which represents a structural biomarker of LA function, might lead to brain amyloid deposition through either changes in perfusion or promoting embolism. LA enlargement has been associated with AF, but the directionality of a potential cause-effect relationship has not been established. There may be a multihit phenomenon, with literature suggesting that in patients with Alzheimer disease, those with the APOE e4 allele and permanent AF have lower Mini-Mental State Examination scores and the highest risk of cognitive deterioration when compared with similar individuals without AF.[14]

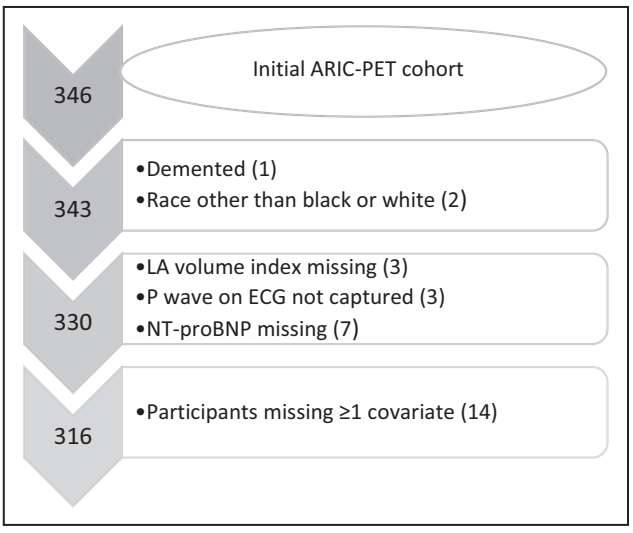

Figure. Study flow diagram demonstrating how final sample size was achieved (N=316).
ARIC-PET indicates Atherosclerosis Risk in Communities–Positron Emission Tomography; LA, left atrial; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

A state of atrial cardiopathy is increasingly recognized as an important impetus for thrombi, and subsequent embolism, even without the development of AF. We therefore cautiously suggest that an earlier diagnosis of LA dysfunction, using a compilation of biomarkers, such as atrial size, measured herein by LAVI, may identify a cohort at risk for a pathologic precursor of Alzheimer disease. Further research into this question in ARIC study is ongoing, with recent data suggesting that participants with LA enlargement and AF had significantly lower global cognition, whereas those with AF or LA enlargement alone did not, compared with individuals with normal LA size and no AF.[15]

We certainly do not imply causality, and importantly acknowledge that although no significant interaction term, the role of APOE e4 carriage is thought provoking, suggesting atrial cardiopathy may be more important for noncarriers. In addition, although the data for cerebral amyloidosis are robust, there is currently insufficient evidence to support its involvement in an atrial cardiopathy.

Important ongoing work will help determine if changes in cardiac structure and function precede, or occur simultaneously with, brain amyloid deposition.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Participant demographics, stratified by cognitive status* (N=316).

Cognitive Status	Mild cognitive impairment (N=85)	Cognitively normal (N=231)	P-value
Age (years old), mean (SD)	76 (5)	77 (5)	0.08
Female	135 (58)	42 (49)	0.15
Black race	99 (43)	36 (42)	0.94
History of ever smoking	134 (58)	48 (57)	0.81
Hypertension	167 (72)	66 (78)	0.34
Low density lipoprotein (mg/dL), mean (SD)	107 (33)	102 (31)	0.26
Diabetes	72 (31)	36 (42)	0.06
Body mass index (kg/m2), mean (SD)	29 (5)	29 (5)	0.88
Prevalent coronary heart disease	20 (9)	5 (6)	0.42
Estimated glomerular filtration rate (mL/min/1.73 m2), mean (SD)	71 (17)	71 (18)	0.92
Education level			
<High School	35 (15)	16 (19%)	0.73
High School Graduate or equivalent	100 (43)	35 (41%)	
>High school	96 (41)	34 (40)	
Prevalent atrial fibrillation	13 (6%)	4 (5%)	0.75
APOE e4	66 (29)	32 (38%)	0.13

* Values are N (%) unless otherwise specified; Hypertension was defined as systolic blood pressure ≥140, diastolic blood pressure ≤90 or antihypertensive medication use, Diabetes was defined as a hemoglobin A1C ≥6.5%

Table S2. Odds of elevated global cortical cerebral amyloid by florbetapir PET (SUVR>1.2) by cardiac variable, stratified by cognitive status (participants with dementia ineligible).

Cardiac Independent Variable	MCI (N=81)		Cognitively normal (N=233)		P-interaction term
	OR	95% CI	OR	95% CI	
LAVI (ml/m2) ≥34 ml/m2	8.36	0.88-79.66	1.77	0.77-4.05	0.26
P-wave terminal force >5000 uV x ms	1.96	0.14-27.11	0.55	0.16-1.90	0.44
serum NT proBNP>250 pg/mL	0.81	0.19-3.52	2.77	1.15-6.65	0.43
Atrial Cardiopathy	2.04	0.51-8.18	1.77	0.98-3.37	0.26
Prevalent Atrial fibrillation	0.55	0.15-2.01	3.44	0.21-57.36	0.31

MCI=mild cognitive impairment, LAVI=left atrial volume index, OR=odds ratio, CI=confidence interval

Adjustment model: age, race (black or white), sex, education level (<high school, high school graduation/equivalent, >high school), hypertension (systolic blood pressure ≥140mm Hg, diastolic blood pressure ≥90mm Hg or antihypertensive medication use), diabetes mellitus (hemoglobin A1C ≥6.5%), low density lipoprotein (mg/dL), smoking history (ever versus never), body mass index (kg/m2), prevalent coronary heart disease, estimated glomerular filtration rate-creatinine (mL/min/1.73 m2), prevalent atrial fibrillation, APOE e4