Cerebral small vessel disease associated with atrial fibrillation among older adults: a population-based study

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Abstract

Background and Purpose: Cerebral small vessel disease (SVD), as a potential mechanism underlying the association between atrial fibrillation (AF) and dementia, remains poorly investigated. In this cohort study, we sought to examine the association between AF and cerebral SVD markers among older adults.

Methods: Data on 336 participants (age ≥60 years, mean 70.2 years; 60.2% women) free of dementia, disability, and cerebral infarcts were derived from the population-based Swedish National study on Aging and Care in Kungsholmen. Structural brain MRI examinations were performed at baseline (2001-2004) and follow-ups (2004-2007 and 2007-2010). MRI markers of cerebral SVD included perivascular spaces (PVS), lacunes, and volumes of white matter hyperintensities (WMH), lateral ventricles, and total brain tissue. AF was assessed at baseline and follow-ups through clinical examinations, electrocardiogram, and medical records. Data were analyzed using linear mixed-effects models.

Results: At baseline, 18 persons (5.4%) were identified to have prevalent AF and 17 (5.6%) developed incident AF over the 6-year follow-up. After multivariable adjustment, AF was significantly associated with a faster annual increase in WMH volume (β coefficient=0.45; 95% CI: 0.04–0.86) and lateral ventricular volume (0.58; 0.13–1.02). There was no significant association of AF with annual changes in PVS number (β coefficient=0.53; 95% CI: -0.27–1.34) or lacune number (-0.01; -0.07–0.05).

Conclusions: Independent of cerebral infarcts, AF is associated with accelerated progression of white matter lesions and ventricular enlargement among older adults.

Non-standard abbreviations

AF	Atrial fibrillation
APOE	Apolipoprotein E gene
SVD	Small vessel disease
PVS	Perivascular spaces
WMH	White matter hyperintensities
MMSE	Mini-mental state examination
SNAC-K	Swedish National study on Aging and Care in Kungsholmen
SD	Standard deviation
CI	Confidence interval

Introduction

Increasing evidence has suggested an association of atrial fibrillation (AF) with cognitive dysfunction even in the absence of clinical stroke.[1] The potential mechanisms underlying this association include cerebral thromboembolism and hypoperfusion, which have been linked with cerebral small vessel disease (SVD).[2,3]

Current evidence linking AF to cerebral SVD markers come largely from cross-sectional studies with mixed findings, where some studies reported an association of AF with white matter hyperintensities (WMH) and brain atrophy,[4,5] while others did not.[6,7] To date, very few longitudinal studies have examined a spectrum of cerebral SVD markers to comprehensively understand the potential contribution of AF to structural brain damage in old age. Thus, this population-based cohort study aimed to investigate the longitudinal associations of AF with multiple cerebral SVD markers among community-dwelling older adults.

Methods

Data supporting this study will be available upon approval by the data management committee at the Aging Research Center, Karolinska Institutet. The reporting of this study conforms to the STROBE statement (for the STROBE checklist of this study, please see https://www.ahajournals.org/journal/str).

Data were derived from the population-based Swedish National study on Aging and Care in Kungsholmen (SNAC-K), which consists of a random sample of people aged ≥60 years in the Kunsholmen district of central Stockholm, Sweden.[1] Details of the sampling and data collection procedures are described in the online-only materials (please see

https://www.ahajournals.org/journal/str). During 2001-2003, SNAC-K participants who were non-institutionalized, non-disabled, and without dementia were invited for a structural brain MRI examination, and 555 individuals were scanned. Follow-up MRI assessments were performed every 3 years for older cohorts (≥78 years, re-examined in 2004-2007 and 2007-2010) and after 6 years for younger cohorts (60-72 years, re-examined in 2007-2010). Participants with cerebral infarcts on MRI at either baseline or follow-ups were excluded. **Figure 1** shows the flowchart of the study population. SNAC-K was approved by the Ethics Committee at the Karolinska Institutet or the Regional Ethics Review Board in Stockholm. All participants provided written informed consents.

AF was identified through electrocardiogram examination and physician's diagnosis at each study visit or the patient register (ICD-10 code: I48). Once AF was identified, participants were considered to have a history of AF throughout the follow-up. Covariates included education, alcohol consumption, smoking, physical activity, hypertension, diabetes, dyslipidemia, coronary heart disease, heart failure, the Mini-Mental State Examination score, and APOE ε4 allele.

Participants were scanned on a Philips Intera 1.5T MRI Scanner (Eindhoven, The Netherlands) at baseline and follow-ups (please see https://www.ahajournals.org/journal/str). Cerebral infarcts, lacunes, and PVS were visually assessed by a trained neurologist (Y.L.). T1-weighted images were automatically segmented into gray matter, white matter, and cerebrospinal fluid, and all segmentations were visually inspected by a specialist (G.K.). Total brain tissue volume was calculated by adding up gray matter and white matter volume. The lateral ventricles were automatically segmented, and their volumes were estimated using the ALVIN toolbox.[8] Global WMH were manually drawn on FLAIR images, and their

volumes were computed. We corrected all volumetric measurements using total intracranial volume.

Statistical analysis

Linear mixed-effects models were performed to estimate the annual changes in the number of PVS and volumes of WMH, total brain tissue, and lateral ventricles over the follow-up period in association with AF; AF was treated as a time-varying variable accounting for both prevalent and incident AF cases. Stata 15.0 (StataCorp LLC, College Station, TX, USA) was used for all analyses.

Results

At baseline, the mean age of the 336 participants free of cerebral infarcts was 69.7 (SD 8.6) years and 61.3% were women. Eighteen (5.4%) participants were identified to have prevalent AF and 17 (5.6%) developed incident AF over the follow-up. Participants with prevalent AF were older and more likely to have heart failure than those without (**Table 1**).

During the 6-year follow-up, AF (as a time-varying variable) was not significantly associated with annual changes in either PVS number (β coefficient=0.53; 95% CI: -0.27–1.34) or lacune number (-0.01; -0.07–0.05), after controlling for demographics, lifestyles, vascular disorders, and APOE ε4 allele. People with AF had significantly faster annual increase in WMH volume (β coefficient=0.45, 95% CI: 0.04–0.86) and lateral ventricular volume (0.58; 0.13–1.02) than those without AF (**Table 2**).

Discussion

In this population-based study of older adults free of cerebral infarcts, we found that AF was associated with a faster annual increase in WMH volume and lateral ventricular volume. The findings of AF in association with accelerated progression of white matter lesions and ventricular enlargement are consistent with two population-based studies in Europe,[4,5] but not the studies in USA.[6,7] In addition, our study is the first to evaluate the longitudinal association of AF with PVS and lacunes, and we found no evidence that AF was associated with the development of PVS or lacunes over time.

Strengths of our study include the population-based design, repeated assessments of various SVD MRI markers, and comprehensive measurements of AF and covariates. Our study also has limitations. Participants in the SNAC-K MRI subsample were relatively younger and healthier than the target population and additional participants were further excluded due to lack of follow-up MRI data, suboptimal image quality or brain pathologies (e.g., infarcts and tumors). Thus, our findings on the association between AF and cerebral SVD markers might not be generalizable to the general population of older adults. In addition, we could not assess the association of AF with microinfarcts and microbleeds due to the lack of relevant MRI sequences for these markers.

In conclusion, independent of cerebral infarcts, AF was associated with accelerated progression of white matter lesions and ventricular enlargement among older adults. Future investigations are warranted to examine to what extent cerebral SVD markers mediate the relationship between AF and cognitive outcomes.

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Disclosures

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Supplemental materials

Expanded Materials & Methods

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Figure 1. Flowchart of the participants in the SNAC-K MRI study, 2001-2003 to 2007-2010.

Table 1. Baseline characteristics of the study population by atrial fibrillation status

Characteristics	Total sample (n=336)	Atrial fibrillation at baseline		
		No (n=318)	Yes (n=18)	p value
Age (years), mean (SD)	69.7 (8.6)	69.5 (8.6)	74.0 (8.4)	0.015
Women	206 (61.3)	197 (62.0)	9 (50.0)	0.311
Education (years)				0.359
Elementary school (<8)	30 (8.9)	28 (8.8)	2 (11.1)	
High school (8-12)	148 (44.1)	143 (45.0)	5 (27.8)	
University or above (>12)	158 (47.0)	147 (46.2)	11 (61.1)	
Current smoking	37 (11.0)	37 (11.7)	0 (0.0)	0.124
Alcohol consumption				0.678
Never or occasional	67 (19.9)	63 (19.8)	4 (22.2)	
Light to moderate	205 (61.0)	193 (60.7)	12 (66.7)	
Heavy	64 (19.1)	62 (19.5)	2 (11.1)	
Physical inactivity	56 (16.7)	53 (16.7)	3 (16.7)	1.000
Body mass index (kg/m^2), mean (SD)	26.0 (4.0)	26.0 (4.1)	26.2 (3.2)	0.412
Hypertension	216 (64.3)	205 (64.5)	11 (61.1)	0.773
Dyslipidemia	190 (56.6)	179 (56.3)	11 (61.1)	0.688
Diabetes mellitus	20 (6.0)	20 (6.4)	0 (0.0)	0.752
Heart failure	13 (3.9)	9 (2.8)	4 (22.2)	<0.001
Coronary heart disease	26 (7.7)	26 (8.2)	0 (0.0)	0.207
MMSE score, mean (SD)	29.2 (1.1)	29.2 (1.0)	28.9 (1.7)	0.122

Data are n (%), unless otherwise specified. SD indicates standard deviation; MMSE, Mini-mental state examination.

Table 2. Longitudinal association of atrial fibrillation (as a time-varying variable) with average annual changes in MRI measurements of cerebral SVD markers, 2001-2003 to 2007-2010.

MRI measures (as outcomes)	**No. of subjects**	**β coefficient (95% confidence interval)**	
		Model 1*	**Model 2***
Number of perivascular spaces	336	0.52 (-0.29–1.32)	0.53 (-0.27–1.34)
Number of lacunes	336	-0.01 (-0.07–0.05)	-0.01 (-0.07–0.05)
WMH volume (mL)	248	0.47 (-0.01–0.95)	0.45 (0.04–0.86)
Lateral ventricular volume (mL)	248	0.57 (0.13–1.01)	0.58 (0.13–1.02)
Total brain tissue volume (mL)	248	-1.22 (-3.77–1.33)	-1.17 (-5.02–4.67)

*Model 1 was adjusted for age, sex, and education; Model 2 was additionally adjusted for smoking, alcohol consumption, physical inactivity, body mass index, hypertension, diabetes, dyslipidemia, heart failure, coronary heart disease, and APOE ε4 allele.

SVD indicates small vessel disease; WMH, white matter hyperintensity; mL, milliliter.