ESC European Society of Cardiology

European Heart Journal (2025) **00**, 1–11
https://doi.org/10.1093/eurheartj/ehaf036

CLINICAL RESEARCH
Arrhythmias

Atrial fibrillation catheter ablation, brain glymphatic function, and cognitive performance

Jiahuan Guo [1,†], Zhe Zhang [2,3,†], Xu Meng [4,†], Jing Jing [1,2,3], Yiran Hu [5,6], Yan Yao [5], Ligang Ding [5,*], Lihui Zheng [5,*], and Xingquan Zhao [1,3,7,8,*]

[1]Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, 119 South Fourth Ring West Road, Fengtai District, 100070 Beijing, China; [2]Tiantan Neuroimaging Center of Excellence, Beijing Tiantan Hospital, Capital Medical University, 119 South Fourth Ring West Road, Fengtai District, 100070 Beijing, China; [3]China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, 119 South Fourth Ring West Road, Fengtai District, 100070 Beijing, China; [4]Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Sciences and Peking Union Medical College, 167 North Lishi Road, Xicheng District, 100037 Beijing, China; [5]Arrhythmia Center, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, 167 North Lishi Road, Xicheng District, 100037 Beijing, China; [6]Department of Cardiology and Macrovascular Disease, Beijing Tiantan Hospital, Capital Medical University, 119 South Fourth Ring West Road, Fengtai District, 100070 Beijing, China; [7]Research Unit of Artificial Intelligence in Cerebrovascular Disease, Chinese Academy of Medical Sciences, 119 South Fourth Ring West Road, Fengtai District, 100070 Beijing, China; and [8]Center of Stroke, Beijing Institute for Brain Disorders, 119 South Fourth Ring West Road, Fengtai District, 100070 Beijing, China

Received 22 June 2024; revised 21 September 2024; accepted 21 January 2025

See the editorial comment for this article 'Taking out the trash: the role of glymphatic function on cognitive function in patients with atrial fibrillation', by T. Jared Bunch, https://doi.org/10.1093/eurheartj/ehaf040.

Abstract

Background and Aims It remains unknown whether the brain glymphatic system, which is driven by the heartbeat-driven pulsation of arteries and is responsible for cerebral waste clearance, is impaired in atrial fibrillation (AF) and mediates cognitive dysfunction related to AF. The aim of this study was to assess brain glymphatic alterations in AF, their role in cognitive function, and whether catheter ablation can improve glymphatic activity.

Methods In this case-control and prospective before–and–after study, patients with AF and healthy controls (HCs) were enrolled. Participants underwent brain magnetic resonance imaging and a comprehensive neuropsychological battery. Glymphatic activity was quantified by diffusion tensor image analysis along the perivascular space (DTI-ALPS) index. Magnetic resonance imaging was repeated after surgery in patients who underwent ablation.

Results Overall, 87 patients with AF and 44 HCs were enrolled. Compared with HCs, patients with AF had a lower ALPS index ($P = .016$). Nonparoxysmal AF patients showed lower ALPS index than both HCs ($P = .002$) and paroxysmal AF patients ($P = .044$). A lower ALPS index was associated with worse scores of Trail Making Test, Digit Symbol Substitution Test, Digit Span Test, and Stroop Colour and Word Test (all $P < .05$). Mediation analyses revealed that glymphatic activity was a mediator between AF and cognitive decline. Among the 50 patients who underwent ablation therapy, DTI-ALPS index was improved after surgery ($P = .015$).

Conclusions Brain glymphatic function measured by DTI-ALPS index was impaired in patients with AF, mediates the association between AF and cognitive decline, and was improved after ablation therapy.

* Corresponding authors. Tel: +86-010-5997-5549, Email: zxq@vip.163.com (X.Z.); Tel: +86-010-8832-2403, Email: zhenglihui@263.net (L.Z.); Tel: +86-010-8832-2402, Email: dlgang101@163.com (L.D.)
† The first three authors contributed equally to the study and should be considered as first authors.

Structured Graphical Abstract

Key Question

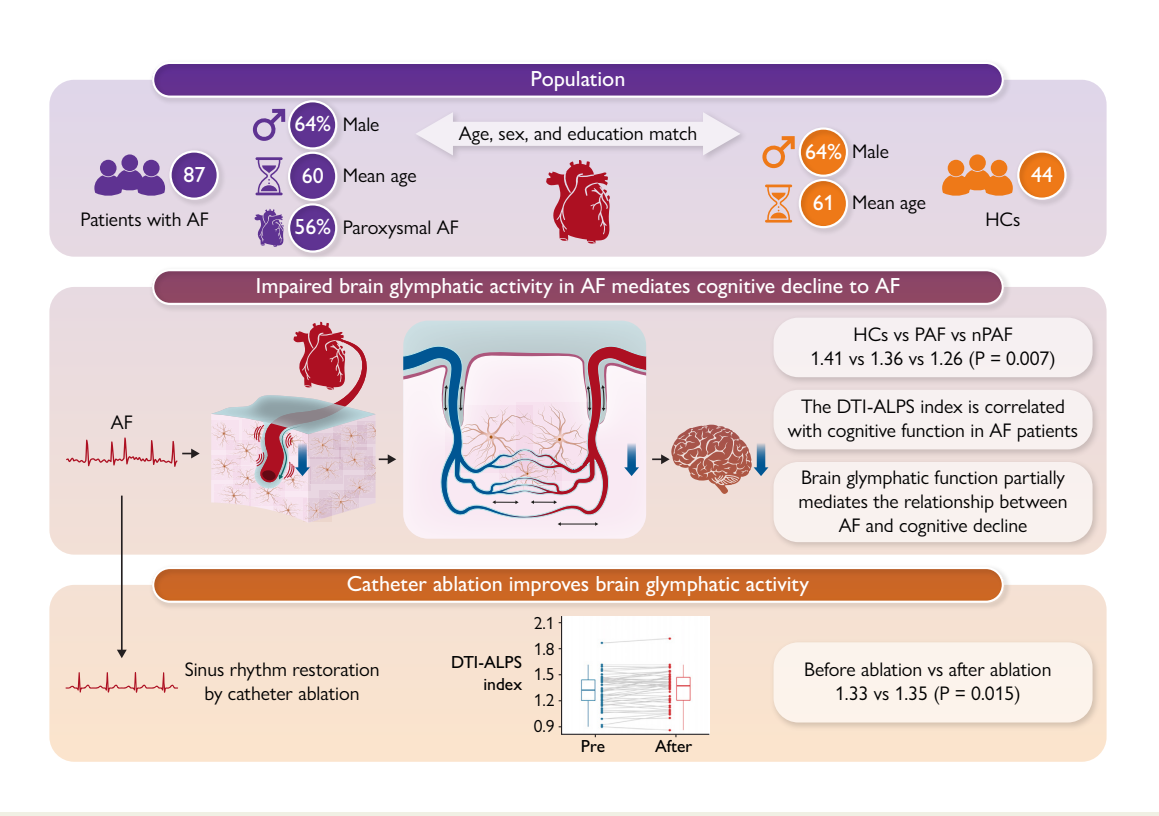
The glymphatic system is a recently discovered clearance system in the brain responsible for cerebrospinal fluid flow. Is brain glymphatic function impaired in atrial fibrillation (AF) patients? Does it mediate the cognitive dysfunction related to AF? Does sinus rhythm restoration by catheter ablation improve glymphatic activity?

Key Finding

Patients with AF showed reduced brain glymphatic activity. Lower glymphatic activity was correlated with cognitive decline and served as a significant mediator in the relationships between AF and cognitive dysfunction. Brain glymphatic activity improved after catheter ablation.

Take Home Message

Brain glymphatic function is impaired in AF, and may mediate the association between AF and cognitive dysfunction. Sinus rhythm restoration by catheter ablation may be a promising method to protect brain glymphatic function.



The brain glymphatic activity is impaired in patients with atrial fibrillation (AF), correlates with cognitive function, and mediates the relationship between AF and cognitive decline. Glymphatic activity was improved after catheter ablation in patients with AF. HCs, health controls; PAF, paroxysmal AF; nPAF, nonparoxysmal AF; DTI-ALPS, diffusion tensor image analysis along the perivascular space.

Keywords Atrial fibrillation • Catheter ablation • Glymphatic function • Cognitive function

Introduction

Atrial fibrillation (AF) is the most common form of cardiac arrhythmia and is a well-known risk factor for cerebrovascular disease and mortality.[1] Over the past decade, growing evidence has suggested that AF is also associated with cognitive impairment and dementia, regardless of the presence of stroke, and is independent of shared vascular risk factors.[2–4] Notably, AF increases the probability of developing not only all-cause dementia and vascular dementia but also Alzheimer's disease (AD).[3,5] AF has also been found to contribute to cognitive decline in patients with AD.[6] These findings suggest that relation between AF and dementia is multifactorial and is not limited to thromboembolic and cerebrovascular events. Other mechanisms contributing to pathological neurodegenerative changes may also play important roles and warrant further investigation. However, the underlying mechanisms remain largely unknown.

Impaired brain glymphatic function may explain part of the association between AF and cognitive dysfunction, but investigations are

currently lacking. The glymphatic system is a recently discovered, highly organized clearance system in the brain that is responsible for cerebrospinal fluid (CSF) flow into the brain parenchyma along the arterial perivascular space (PVS) and the transport of extracellular waste.[7] Recently, both animal and human neuroimaging studies have suggested that insufficient glymphatic clearance contributes to the accumulation of neurotoxic proteins and plays an important role in the progression of cognitive dysfunction.[8–10]

Notably, normal cardiac pulsation has been proposed to play a potential role in glymphatic function and the clearance of neurotoxic waste from the brain.[11] Fluid flow along the PVS is thought to be facilitated by mechanical forces created by cardiac-dependent pulsatility.[12] Irregular heartbeats would affect vascular wall wave dynamics and disrupt the periodicity of the arteriolar systolic pulsation wave. This arrhythmia-caused disturbance in the perivascular convection may reduce glymphatic clearance by decreasing CSF flow and altering CSF flow rhythmicity, leading to the accumulation of neurotoxic agents.[13] Based on previous evidence, it is plausible that glymphatic activity may be impaired in patients AF via irregular heartbeats and further contributes to neurodegeneration and cognitive decline in AF.

Against this background, a topic of interest is whether glymphatic function is impaired in patients with AF and mediates the association between AF and cognitive dysfunction and whether restoration of sinus rhythm can improve glymphatic function in patients with AF. However, it has not yet been explored in human studies. Therefore, the purpose of this study was to assess brain glymphatic function in individuals with different types of AF and its relevance to cognitive function, as well as alterations in glymphatic function after the restoration of sinus rhythm by catheter ablation.

Methods

Study design and population

Patients who presented with AF were prospectively and consecutively screened and examined between July 2023 and September 2024. The inclusion criteria were as follows: (i) aged 18–80 years and (ii) diagnosed with AF. Patients were excluded if they (i) had previous organic or degenerative brain diseases (including previous stroke, transient ischaemic attack, neurodegenerative diseases, encephalitis, head trauma, hydrocephalus, brain tumour, epilepsy, or dementia); (ii) had severe cardiac diseases other than AF (including heart failure, myocardial infarction, valvular disease, pericardial disease, hypertrophic cardiomyopathy, dilated cardiomyopathy, congenital heart disease, and other types of arrhythmia); (iii) had undergone any previous ablation, or other surgical therapy for AF; (iv) had intracranial or carotid arterial occlusion or stenosis > 50%; (v) had a depressive state or mental illness; (vi) were currently using sedatives, analgesics, anxiolytics, antidepressants, or other medications that may affect cognitive function; (vii) had previously consumed heavy amounts of alcohol over long periods; (viii) had severe kidney or liver diseases, malignant tumours, or any disease that limits life expectancy to less than 1 year; (ix) were pregnant or within 30 days after delivery; (x) had colour blindness or colour perception issues, difficulties in communication, or auditory impairment that affect cognitive assessment; or (xi) had contraindications for magnetic resonance imaging (MRI), did not agree to undergo neuroimaging, or failed to complete brain MRI due to excessive motion. Patients were classified into paroxysmal and nonparoxysmal (including persistent and permanent) AF according to the recommended definitions.[14] During the study period, 44 healthy controls (HCs) matched for age, sex, and years of education were recruited and subjected to the same exclusion criteria as the AF patients. Catheter ablation was performed in a subset of patients with AF according to the clinicians' suggestions and patient willingness. The detailed surgical procedures are described in the Supplementary data online. Magnetic resonance imaging was repeated for 50 patients with AF who had undergone ablation therapy and sinus rhythm was successfully restored within 7 days after surgery (see Supplementary data online, *Figure S1*). The study protocol was approved by the institutional review board of Beijing Tiantan Hospital (no. KY2023-163-01). All research procedures adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all patients or their legal guardians.

Neurocognitive assessment protocol

Neurocognitive performance was assessed with a comprehensive and thorough standardized test battery administered by a trained neurologist. The test battery was designed to assess a full range of cognitive function domains. Global cognitive function was assessed by the Montreal Cognitive Assessment (MoCA). Verbal memory was assessed by the Rey auditory verbal learning test (RAVLT, immediate recall and delayed recall); visual spatial ability and memory were evaluated by the Rey–Osterrieth Complex Figure test (ROCF, immediate recall and delayed recall). Attention and executive function were assessed by the Trail Making Test Part A (TMT-A), Trail Making Test Part B (TMT-B), Digit Symbol Substitution Test (DSST), Digit Span Test (DST, forward and backward), and Stroop Colour and Word Test (SCWT). Language was assessed by the Animal Fluency Test (AFT) and the Boston Naming Test (BNT). The cognitive evaluations and information collection lasted approximately 90 min. Additional details regarding the cognitive assessments are provided in Supplementary data online, *Table S1*.

Magnetic resonance imaging protocol

All enrolled study participants underwent 3.0 T MRI (NX, United Imaging Healthcare, Shanghai, China) scan using a 64-channel head–neck coil; standard electrocardiography was conducted for each participant before initiating MRI to identify whether the patients were experiencing fibrillation. For catheter ablation patients, MRI was performed within 3 days before surgery and within 7 days after surgery. The imaging protocols for the MRI scans included 3D T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) sequence, susceptibility-weighted imaging (SWI) sequence, and multi-shell diffusion-weighted imaging (DWI) sequence. More detailed technical information for MRI is presented in Supplementary data online.

The diffusion tensor image analysis along the PVS (DTI-ALPS) index is used to evaluate perivascular water diffusivity at the level of the lateral ventricular body where the direction of perivascular water flow is along the medullary veins and reflects the ability of the brain to drive fluids from subcortical regions into the lateral ventricles.[15,16] A similar methodology was implemented as in previous studies for DTI-ALPS processing and measurement[8,15–19] on the DWI data set in this study. Diffusion tensor image preprocessing was performed using the FMRIB Software Library (FSL; version 6.0.5.1; available at https://fsl.fmrib.ox.ac.uk/). Spherical regions of interest (ROIs) in the FA template with 5 mm diameters were used. To assess the robustness of the results, sensitivity analyses were performed using ROIs with 10 mm diameters. The technical information for the processing of the DTI-ALPS index is detailed in the Supplementary data online. The global ALPS index was calculated by the mean of ALPS indexes from both hemispheres. The pipeline for measuring the ALPS index is shown in *Figure 1*.

T1-weighted images were analysed with the Computational Anatomy Toolbox (CAT; version 12.8.2) implemented in Statistical Parametric Mapping 12 (SPM12; version 7771, available at https://www.fil.ion.ucl.ac.uk/spm/). Images were corrected for bias-field inhomogeneity; segmented into grey matter, white matter, and CSF volumes; and spatially normalized to MNI space. The grey matter volume (GMV) ratio was obtained by calculating the ratio of GMV to intracranial volume.

Statistical analysis

Clinical data were compared among the AF and control groups using the χ^2 test or Fisher's exact test for categorical variables. For continuous variables,

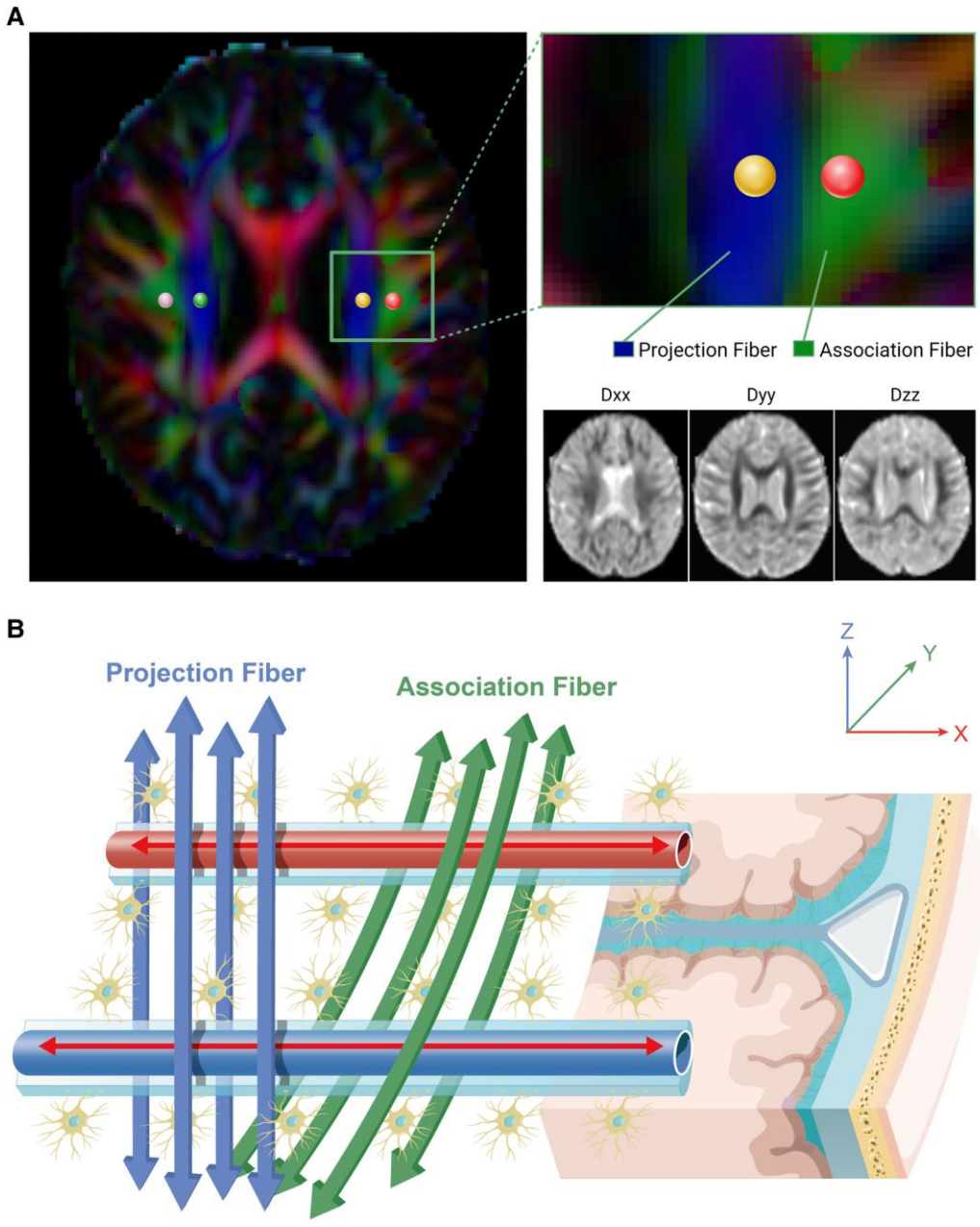


Figure 1 Schematic illustration of the MRI data pre-processing procedure and the principle underlying the diffusion tensor image analysis along the perivascular space. (*A*) Placement of a region of interest, colour-coded FA map, and (*B*) schematic illustration of diffusion tensor image analysis along the perivascular space. Perivascular water flows perpendicular to projection neural fibres. Diffusivity along the *x*-axis at these areas can reflect perivascular glymphatic flows

Student's *t*-test and the Mann–Whitney *U* test were used for comparisons between groups. Between-group differences in the DTI-ALPS index were evaluated using a general linear model. Age, years of education, and the GMV ratio were used as covariates. To assess the association between the DTI-ALPS index and neuropsychological test scores in patients with AF, partial correlation analyses were performed adjusted for age, sex, years of education, and GMV ratio. Mediation analysis was performed using PROCESS for SPSS software (version 25.0 for Windows, IBM) with a level of confidence of 95% and 5000 bootstrap samples to explore the potential of the ALPS index as a mediator between AF and cognitive function. Age, sex, education years, and GMV ratio were used as covariates. Total, direct, and indirect effects were evaluated, and the percentage of mediation (Pm) was calculated as the indirect effect divided by the total effect. Changes in the DTI-ALPS index after ablation therapy were evaluated using paired *t*-tests to compare the baseline conditions with those after ablation. A sensitivity analysis was conducted using different sizes of ROIs to evaluate the DTI-ALPS index. Statistical analysis and data visualization were performed using SPSS software (version 25.0 for Windows, IBM) and R (version 4.3.3). All the statistical analyses were two-tailed, and statistical significance was indicated if the $P < .05$.

Results

Demographic and clinical characteristics

A total of 87 patients with AF and 44 HCs were included. All patients completed the clinical screening, neurocognitive assessment, and MRI acquisition. In the analysis of the changes in DTI-ALPS index before and after ablation therapy, 50 patients with AF were included. All patients completed MRI acquisition within 3 days before surgery and within 7 days after surgery.

As shown in *Table 1*, there were no significant differences in age, sex, years of education, mean total sleep time at night, smoking status, history of hypertension, diabetes, dyslipidaemia and coronary heart disease, antihypertensive, antidiabetic and lipid-lowering agents use, and baseline heart rate between groups. Compared with HCs, patients with AF were more likely to use anticoagulant agents, antiarrhythmic agents, and beta-blockers. Compared with HCs, patients with AF had lower MoCA (27.0 vs. 23.0, standardized difference 1.45, $P < .001$), RAVLT-immediate recall (42.2 vs. 29.8, standardized difference 1.43, $P < .001$), RAVLT-delayed recall (7.5 vs. 4.0, standardized difference 1.25, $P < .001$), ROCF-immediate recall (22.4 vs. 17.1, standardized difference .72, $P < .001$), ROCF-delayed recall (21.6 vs. 16.6, standardized difference .69, $P < .001$), DSST (50.9 vs. 39.2, standardized difference .93, $P < .001$), DST-forward (9.0 vs. 8.0, standardized difference .88, $P < .001$), DST-backward (6.0 vs. 4.0, standardized difference 1.28, $P < .001$), AFT (22.0 vs. 17.0, standardized difference .91, $P < .001$), and BNT (25.0 vs. 22.0, standardized difference .66, $P = .002$) scores and higher TMT-A (39.9 vs. 48.7, standardized difference .61, $P = .001$), TMT-B (49.4 vs. 66.6, standardized difference .98, $P < .001$), SCWT-A (23.8 vs. 26.4, standardized difference .59, $P = .006$), SCWT-B (34.0 vs. 42.1, standardized difference .67, $P = .001$), and SCWT-C scores (69.4 vs. 81.2, standardized difference .69, $P < .001$). These results illustrated that cognitive function in different domains was impaired in stroke-free patients with AF.

Table 1 Baseline demographic and clinical features of the study population

Characteristic	HC ($n = 44$)	AF ($n = 87$)	*P*-value
Age, y	60.6 (9.3)	60.4 (10.4)	.910
Male, *n* (%)	28 (63.6)	56 (64.4)	.934
Education years	13.0 (12.0–16.0)	12.0 (9.0–16.0)	.684
Mean total sleep time, h	6.5 (6.0–7.5)	7.0 (6.0–7.5)	.656
Current smoker, *n* (%)	13 (29.5)	15 (17.2)	.105
Medical history, *n* (%)			
Hypertension	21 (47.7)	44 (50.6)	.758
Diabetes	8 (18.2)	15 (17.2)	.894
Dyslipidaemia	15 (34.1)	24 (27.6)	.442
Coronary heart disease	6 (13.6)	10 (11.5)	.724
Heart failure	0 (0)	0 (0)	
Concomitant medication use, *n* (%)			
Anticoagulant agents	0 (0)	63 (72.4)	<.001
Antiarrhythmic agents	0 (0)	11 (12.6)	.016
Beta-blockers	1 (2.3)	51 (58.6)	<.001
Antihypertensive agents	16 (36.4)	41 (47.1)	.241
Antidiabetic agents	6 (13.6)	12 (13.8)	.980
Lipid-lowering agents	14 (31.8)	23 (26.4)	.518
Heart rate, b.p.m	70.0 (68.0–79.3)	74.0 (65.0–80.0)	.819
Time since AF diagnosis, month	-	15.0 (3.0–48.0)	
MoCA	27.0 (26.0–28.0)	23.0 (20.0–25.0)	<.001
RAVLT-immediate recall	42.2 (9.5)	29.8 (7.7)	<.001
RAVLT-delayed recall	7.5 (6.0–10.0)	4.0 (3.0–6.0)	<.001
ROCF-immediate recall	22.4 (7.6)	17.1 (7.2)	<.001
ROCF-delayed recall	21.6 (7.3)	16.6 (7.3)	<.001

Continued

Table 1 *Continued*

Characteristic	HC ($n = 44$)	AF ($n = 87$)	*P*-value
TMT-A	39.9 (11.3)	48.7 (17.0)	.001
TMT-B	49.4 (14.5)	66.6 (20.2)	<.001
DSST	50.9 (13.1)	39.2 (12.1)	<.001
DST-forward	9.0 (8.0–9.0)	8.0 (7.0–8.0)	<.001
DST-backward	6.0 (5.0–7.0)	4.0 (4.0–5.0)	<.001
SCWT-A	23.8 (19.4–28.2)	26.4 (22.9–30.9)	.006
SCWT-B	34.0 (30.4–40.8)	42.1 (34.1–49.9)	.001
SCWT-C	69.4 (56.8–80.2)	81.2 (69.5–92.4)	<.001
AFT	22.0 (19.0–27.0)	17.0 (15.0–21.0)	<.001
BNT	25.0 (22.0–26.0)	22.0 (19.0–25.0)	.002
GMV ratio, %	42.9 (2.7)	42.5 (2.5)	.374

Results are expressed as frequencies for the categorical variables, mean (standard deviation) for normally distributed continuous variables, and median (interquartile range) for continuous variables that do not fit a normal distribution.
AF, atrial fibrillation; AFT, Animal Fluency Test; BNT, Boston Naming Test; DST, Digit Span Test; DSST, Digit Symbol Substitution Test; GMV, grey matter volume; HC, healthy control; MoCA, Montreal Cognitive Assessment; RAVLT, Rey auditory verbal learning test; ROCF, Rey-Osterrieth Complex Figure test; SCWT, Stroop Colour and Word Test; TMT, Trail Making Test.

Between-group differences in diffusion tensor image analysis along the perivascular space index

The averaged DTI-ALPS index according to participant group is summarized in *Table 2*. After adjusting for age, years of education, and GMV ratio, the mean ALPS index was significantly lower in patients with AF than in controls (1.32 vs. 1.41, $P = .016$) (*Figure 2A*). Moreover, when patients with AF were classified into paroxysmal and nonparoxysmal groups according to the AF burden, the ALPS index significantly differed among the three groups, patients with nonparoxysmal AF had the lowest ALPS index, and HCs had the highest (1.26 vs. 1.36 vs. 1.41, $P = .007$) (*Figure 2B*). The ALPS index in patients with nonparoxysmal AF was significantly lower than both HCs (1.26 vs. 1.41, $P = .002$) and patients with paroxysmal AF (1.26 vs. 1.36, $P = .044$). There were no significant differences in the ALPS index between patients with paroxysmal AF and HCs (1.36 vs. 1.41, $P = .192$). Results from the sensitivity analyses were similar to the main results (see Supplementary data online, *Table S2*).

Partial correlation analysis between diffusion tensor image analysis along the perivascular space index and neuropsychological scores in patients with atrial fibrillation

In patients with AF, a lower ALPS index was associated with worse cognitive function in the domains of processing speed, attention, and executive function. Specifically, a lower ALPS index was correlated with lower DSST ($r = .264$; $P = .016$) (*Figure 3A*), DST-forward ($r = .379$; $P < .001$) (*Figure 3B*), and DST-backward ($r = .374$; $P < .001$) (*Figure 3C*) scores and higher TMT-A ($r = -.246$; $P = .025$) (*Figure 4A*), TMT-B ($r = -.253$; $P = .021$) (*Figure 4B*), SCWT-A ($r = -.281$; $P = .010$) (*Figure 4C*), SCWT-B ($r = -.305$; $P = .005$) (*Figure 4D*), and SCWT-C ($r = -.280$; $P = .010$) (*Figure 4E*) scores after adjusting for age, sex, years of education, and GMV ratio. The correlations of the ALPS index with the MoCA, RAVLT, ROCF, AFT, and BNT scores were not significant. Results from the sensitivity analyses were similar to the main results (see Supplementary data online, *Figure S2*).

Mediation analysis

In the mediation analysis for cognitive function (see Supplementary data online, *Figure S3*), after adjusting for age, sex, years of education, and GMV ratio, the ALPS index showed significant mediating effects between AF and the scores of the TMT-A (Pm = 16.3%; indirect effect $\beta = 1.357$, 95% confidence interval (CI): .266, 2.993), TMT-B (Pm = 10.4%; indirect effect $\beta = 1.680$, 95% CI: .400, 3.512), DSST (Pm = 10.1%; indirect effect $\beta = -1.125$, 95% CI: −2.487, −.178), DST-forward (Pm = 17.9%; indirect effect $\beta = -.173$, 95% CI: −.333, −.050), DST-backward (Pm = 12.5%; indirect effect $\beta = -.180$, 95% CI: −.334, −.054), SCWT-A (Pm = 21.3%; indirect effect $\beta = .659$, 95% CI: .168, 1.343), SCWT-B (Pm = 20.9%; indirect effect $\beta = 1.296$, 95% CI: .279, 2.726), and SCWT-C (Pm = 17.1%; indirect effect $\beta = 2.354$, 95% CI: .287, 5.991).

Changes in glymphatic activity after fibrillation ablation

In the subgroup of patients with AF who underwent catheter ablation therapy (32 patients with paroxysmal AF; 18 patients with nonparoxysmal AF), all paroxysmal patients with AF were in sinus rhythm at both the baseline MRI examination before ablation and the repeat MRI examination after ablation. The 18 patients with nonparoxysmal AF were in AF at the baseline MRI examination before ablation and were in sinus rhythm at the time of the repeat MRI examination after ablation. As shown in *Figure 5*, significant improvement in DTI-ALPS index was observed after sinus rhythm restoration by catheter ablation in AF

Table 2 Comparison of the analysis along the perivascular space index among the study groups

Characteristic	Global ALPS index	Right ALPS index	Left ALPS index
HC ($N = 44$)	1.41 (.20)	1.42 (.19)	1.39 (.22)
AF ($N = 87$)	1.32 (.20)	1.34 (.20)	1.29 (.21)
Mean difference (95% CI)[a]	.082 (.016–.148)	.075 (.008–.143)	.089 (.017–.161)
P-value[a] (HC vs. AF)	.016	.028	.015
PAF ($N = 49$)	1.36 (.17)	1.39 (.19)	1.32 (.18)
nPAF ($N = 38$)	1.26 (.22)	1.27 (.21)	1.26 (.23)
P-value[b] (HC vs. PAF vs. nPAF)	.007	.002	.028
Mean difference (95% CI)[c]	.048 (−.025–.121)	.030 (−.043–.103)	.069 (−.011–.149)
P-value[c] (HC vs. PAF)	.192	.414	.093
Mean difference (95% CI)[d]	.128 (.049–.207)	.138 (.058–.217)	.117 (.030–.205)
P-value[d] (HC vs. nPAF)	.002	.001	.009
Mean difference (95% CI)[e]	.079 (.002–.157)	.108 (.030–.185)	.049 (−.036–.134)
P-value[e] (PAF vs. nPAF)	.044	.007	.256

Results are expressed as mean (standard deviation) since variables fit with normal distributions.
AF, atrial fibrillation; CI, confidence interval; HC, healthy control; nPAF, nonparoxysmal AF; PAF, paroxysmal AF.
[a]Comparison between HC and AF groups.
[b]Comparison between HC, PAF, and nPAF groups.
[c]Comparison between HC and PAF groups.
[d]Comparison between HC and nPAF groups.
[e]Comparison between PAF and nPAF groups.

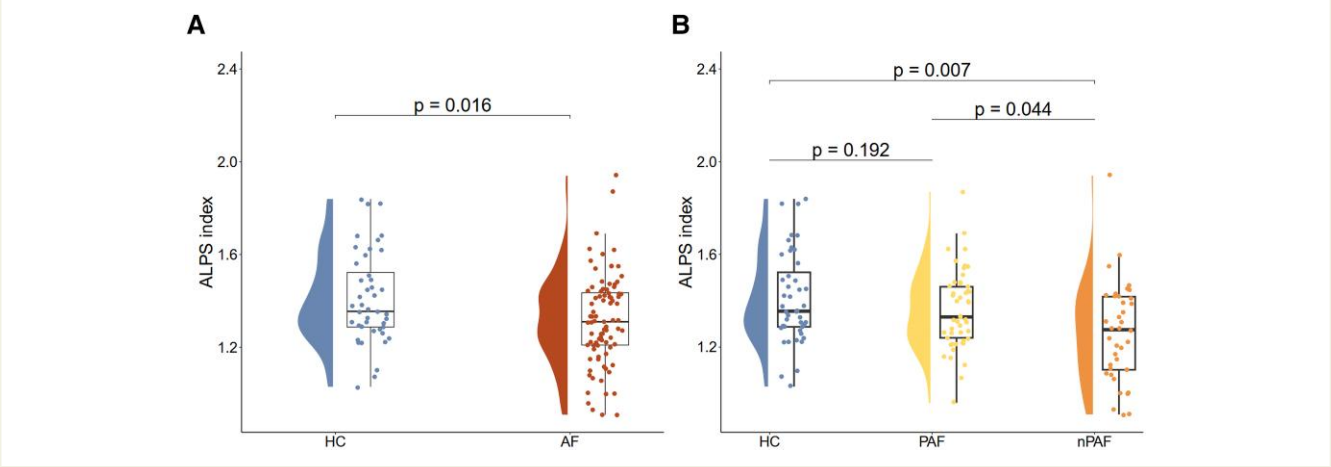


Figure 2 Between-group differences in the diffusion tensor image analysis along the perivascular space index. Violin and box plots of the mean ALPS index among (*A*) healthy controls and atrial fibrillation patients and (*B*) healthy controls, paroxysmal atrial fibrillation patients, and nonparoxysmal atrial fibrillation patients. The lower whisker, bottom of the box, horizontal line, top of the box, and upper whisker indicate the minimum value, first quartile, median, third quartile, and maximum value, respectively

patients (1.33 vs. 1.35, $P = .015$). Result from the sensitivity analysis was similar to the main results (1.25 vs. 1.27, $P = .007$).

Patients were further divided into two groups according to whether the DTI-ALPS index was improved after ablation therapy. As shown in Supplementary data online, *Table S3*, compared with patients with an increased brain glymphatic activity, patients without had a significantly longer time since AF diagnosis (10.5 vs. 48.0, $P = .023$).

Discussion

Using non-invasive MRI measures, this study demonstrated the glymphatic function alterations in patients with AF and its role in the relationship between AF and cognitive dysfunction. Our findings revealed reduced brain glymphatic activity in patients with AF, especially in those with nonparoxysmal AF. A lower DTI-ALPS index was associated with

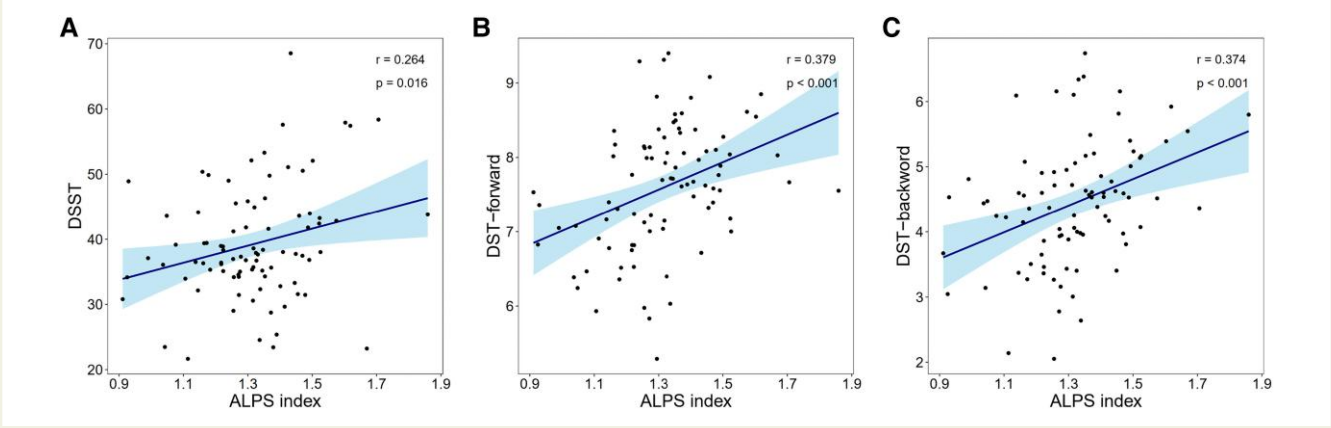


Figure 3 The diffusion tensor image analysis along the perivascular space index showed positive correlations with the scores of the (*A*) Digit Symbol Substitution Test, (*B*) Digit Span Test forward, and (*C*) Digit Span Test backward. The solid line and shadow depict linear regressions with 95% confidence intervals, respectively

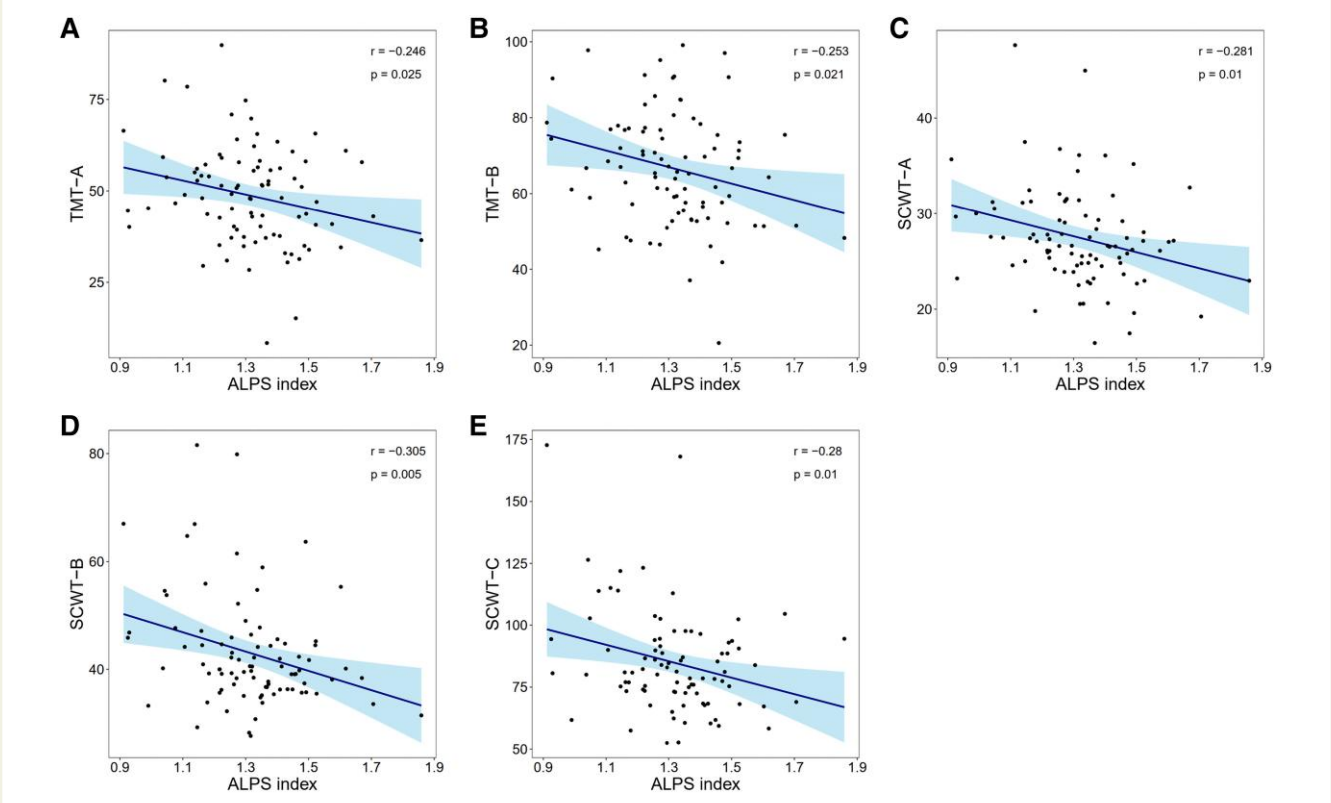


Figure 4 The diffusion tensor image analysis along the perivascular space index showed negative correlations with the scores of the (*A*) Trail Making Test Part A, (*B*) Trail Making Test Part B, (*C*) Stroop Colour and Word Test A, (*D*) Stroop Colour and Word Test B, and (*E*) Stroop Colour and Word Test C. The solid line and shadow depict linear regressions with 95% confidence intervals, respectively

impaired neuropsychological test performance and served as a significant mediator in the relationship between AF and cognitive decline, especially in the domains of processing speed, attention, and executive function. Moreover, the current study also found that the glymphatic activity of the brain was improved after sinus rhythm restoration via catheter ablation. Patients with a shorter time since AF diagnosis may be more likely to achieve glymphatic activity improvement after ablation (*Structured Graphical Abstract*).

The adverse effects of AF on cognitive function have attracted increasing attention over the past decade.[2,3] However, the underlying mechanisms are not fully understood. Although earlier studies hypothesized that the association between AF and cognitive dysfunction

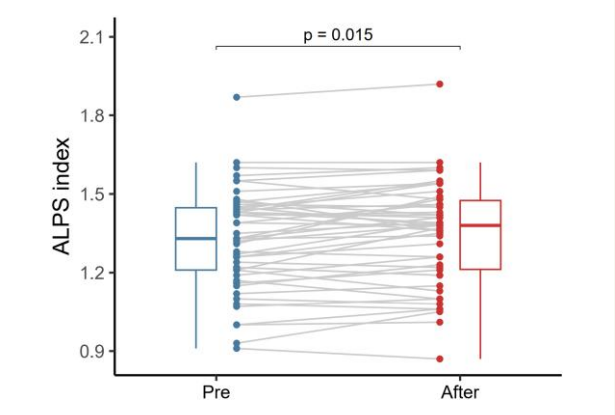


Figure 5 Improvement in diffusion tensor image analysis along the perivascular space index in patients with atrial fibrillation before and after ablation therapy

is mainly a consequence of ischaemic stroke, more recent evidence has suggested that cardiac thromboembolism is not the only mechanism involved.[20] Numerous observational studies have provided growing evidence that AF is associated with an increased risk of cognitive impairment and dementia, even in the absence of stroke.[3,21] Moreover, AF has also been found to be associated with reduced hippocampal volume, cortical atrophy, and increased risk of AD.[22–24] A recent study further demonstrated that AF contributes to cognitive decline in patients with AD and amnestic mild cognitive impairment.[6] These findings indicate that AF can contribute to neurodegeneration and cognitive decline through pathogenesis other than thromboembolism. The current study provides a potential explanation for the contribution of AF to the initiation and acceleration of cognitive dysfunction and dementia. The recently discovered glymphatic system is a whole-brain perivascular network that promotes CSF-interstitial fluid (ISF) exchange and contributes to the clearance of waste products in the brain.[10,25] Numerous studies have confirmed that the glymphatic system is an essential component in the clearance of neurotoxic proteins, such as Aβ and tau, in animal models.[26,27] Recently, several human imaging studies further demonstrated that the ALPS index is significantly correlated with neurotoxic protein accumulation, negative neuronal loss, and the progression of cognitive dysfunction.[9,10] Our results demonstrated that brain glymphatic activity is lower in patients with AF than in HCs, and lower brain glymphatic activity is independently correlated with cognitive function decline even after adjusting for potential covariates. Results of the mediation analysis further demonstrated that brain glymphatic activity is a significant mediator of the relationship between AF and cognitive dysfunction. Of note, although patients with paroxysmal AF were in sinus rhythm before MRI examination, the glymphatic activity was still lower in patients with paroxysmal AF than in HCs, while those with nonparoxysmal AF had the lowest glymphatic activity. These results indicate that the influence of arrhythmia may have an accumulative effect on brain glymphatic activity. Notably, for patients with paroxysmal AF, although we measured participants' heart rhythm and heart rate before MRI examination, tried to complete MRI when the patients were awake and at rest, and further asked if they had heart palpitations or other symptoms during the examination, we did not conduct continuous real-time heart rhythm monitoring during MRI. It is possible that some paroxysmal AF patients might experience short episodes of asymptomatic AF during examination, and we were unable to directly observe the corresponding changes in the glymphatic system when cardiac rhythm changed. Animal experiments could be considered in the future to further explore this via long-term, continuous, real-time monitoring of both cardiac rhythm and glymphatic system simultaneously.

The mechanisms underlying the effect of AF on brain glymphatic function are not fully understood and may involve multiple pathways. First, it has been proposed that fluid exchange in glymphatic system relies on regular cardiac pulsation-driven oscillations. In particular, the ejection pressure of blood from the heart is partly absorbed by the elastic arterial wall, which enlarges the arterial diameter as its pulse wave propagates downstream and is a major driving force of paravascular CSF influx and subsequent CSF-ISF exchange.[12] Heartbeat-driven pial artery pulsations can propel fluorescent microspheres along vessels at the brain surface.[12] In rats, MRI has shown that an increased heartbeat dramatically increases the movement of fluid.[28] These findings suggest that CSF flow is pulsatile and driven primarily by the cardiac cycle and arterial wall motion. Therefore, disturbances in the artery pulsation rhythm, abnormal beating frequency, and decreased arterial pulsatility during arrhythmia in patients with AF may contribute to reduced paravascular flow, further leading to glymphatic dysfunction and insufficient clearance of neurotoxic factors. Second, accumulating evidence suggests that AF may directly affect local haemodynamics and result in repetitive extreme haemodynamic events and disproportionate shear stress variation in the distal cerebral circle during arrhythmia.[29,30] This could activate an atherosclerotic process and arterial wall stiffness and further attenuate arterial wall motion.[29] In addition, CSF transfer into the brain interstitium is facilitated by aquaporin 4 (AQP4) water channels.[8] It has been reported that AQP4 polarization may be altered in AF due to the activation of the renin-angiotensin-aldosterone system, oxidative stress, overloaded calcium, and the release of inflammatory factors.[31,32] This could be another explanation for the glymphatic function impairment in patients with AF. Finally, hypertension might be a risk factor shared by AF and brain glymphatic dysfunction and may mediate the association between them.[12,33] However, in the present study, baseline characteristics demonstrated that there was no significant difference in the prevalence of hypertension between the AF group and the matched HCs. These findings indicate that hypertension appears to be not enough to completely explain the association between AF and brain glymphatic dysfunction.

The above findings may partly explain why anticoagulant therapy alone, although effective for preventing thromboembolism, may not be sufficient to prevent cognitive decline and dementia in patients with AF, especially those with AD.[34–36] Instead, restoring sinus rhythm by catheter ablation may be effective for preserving cognitive function through multiple mechanisms. In a previous meta-analysis, we found that ablation surgery was associated with lower risks of both overall dementia and AD.[37] The current study further demonstrated that the ALPS index was improved after catheter ablation treatment. The improvement of glymphatic activity after catheter ablation suggests that restoring sinus rhythm via catheter ablation may be a potential treatment for improving glymphatic function and metabolic waste clearance, thus protecting cognitive function in patients with AF. Moreover, an intriguing exploratory finding in the present study is that compared with patients with an increased brain glymphatic activity, patients without had a significantly longer time since AF diagnosis, which indicates that earlier ablation therapy for patients with AF may lead to a better therapeutic effect and achieve improvement in brain glymphatic function. These findings provide a clinical rationale for early ablation treatment for patients with AF. In the current guidelines for AF, it has been

proposed that rhythm control can be useful to reduce stroke and mortality in patients with a recent diagnosis of AF (within 1 year), which emphasizes the importance of early rhythm control.[38] Findings in the current study further indicate the potential protective effects of early rhythm control against brain glymphatic and cognitive dysfunction, providing directions for future research.

Our study had several limitations. First, gadolinium-enhanced glymphatic MRI, rather than DTI-ALPS, is currently considered the most direct method for assessing brain glymphatic function. However, the intrathecal enhanced MRI is an invasive examination which requires the intrathecal injection of contrast agent. It is difficult to be performed in patients with AF, especially for those who will receive catheter ablation therapy in the short term. The postoperative re-examination after ablation also seems to be difficult to perform due to its invasive nature. On the other hand, the DTI-ALPS method, which has been widely applied to a series of neurological disorders, enabled us to evaluate brain glymphatic function in patients with AF and its changes before and after ablation. Several studies have demonstrated that the ALPS index is closely related to the classical detection of glymphatic clearance function on intrathecal enhanced MRI, and the ALPS index demonstrated favourable inter-scanner reproducibility, inter-rater reliability, and test-retest repeatability.[19,39,40] Despite this, the results should still be interpreted with caution. Second, the presence of unmeasured or residual confounders in our results cannot be excluded. Although heart rate was assessed for each participant before MRI and we found no significant difference in heart rate between groups, the effects of heart rate variability could not be completely ruled out and is an intriguing future issue. Future studies are needed to further assess the impact of heart rate and heart rate variability on brain glymphatic activity, which may provide further clinical rationale for treatment decisions. Third, continuous, real-time cardiac monitoring was not conducted during MRI scans, which made us unable to observe the corresponding reactions in the brain glymphatic system directly when cardiac rhythm changed. In the meantime, one DTI-ALPS measurement takes about 5 min to scan in this study, which has a lower temporal resolution compared with gadolinium-enhanced glymphatic MRI. Future animal experiments could be considered to further explore this by implementation of long-term, continuous, real-time monitoring of both cardiac rhythm and brain glymphatic system simultaneously. Fourth, this was not a randomized clinical trial and the number of patients who underwent catheter ablation was relatively small, no definitive causality can be concluded. Future clinical trials with larger sample sizes, including a multiethnic sample, are needed to confirm our findings. Finally, the current study only evaluated short-term changes in glymphatic activity after ablation. This part of the analysis was exploratory and needs to be replicated in future studies. Additionally, a very intriguing and important question that remains to be addressed is whether ablation can improve long-term glymphatic function in patients with AF. Despite this, we believe that the changes in glymphatic activity shortly after ablation may be more likely to represent the effect of ablation itself and mildly affected by medication use, lifestyle changes, recurrence of AF, and other confounders that are difficult to accurately characterize and controlled.

Conclusions

In patients with AF, brain glymphatic function measured by DTI-ALPS index was impaired, especially in those with nonparoxysmal AF. Lower brain glymphatic activity was correlated with cognitive decline and served as a significant mediator in the relationship between AF and cognitive dysfunction. Brain glymphatic activity was improved after sinus rhythm restoration by catheter ablation. Our findings provide novel mechanistic insight into the pathogenesis of AF-related cognitive decline and a new potential target for preventing cognitive decline and dementia, which highlights the potential importance of maintaining a regular cardiac rhythm for neurotoxic waste clearance and cognitive function protection.

Acknowledgements

The authors wish to thank Dr Anxin Wang, Dr Binbin Sui, Dr Dandan Wang, and Dr Kaijiang Kang for their guidance on the writing and statistical analysis of the paper.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding authors.

Funding

This study was funded by the National Science and Technology Major Project (grant number 2022ZD0118005), the Beijing Scholar (097), the Risk Factors and Assessment Techniques for Brain Aging (grant number HX-A-2023037), the Central Health Care Research (grant number 2022YB65), and the Ministry of Finance of the People's Republic of China (grant number issued by Finance and Social Security [2015] Document No. 82; [2016] Document No. 50; [2017] Document No. 72; [2018] Document No. 48; [2019] Document No. 77; [2020] Document No. 75; [2021] Document No. 84, [Ministry of Finance]).

Ethical Approval

The study protocol was approved by the Institutional Review Board of Beijing Tiantan Hospital (no. KY2023-163-01). All research procedures adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all patients or their legal guardians.

Pre-registered Clinical Trial Number

The pre-registered clinical trial number is ChiCTR2300076472.

References

1. Al-Khatib SM. Atrial fibrillation. *Ann Intern Med* 2023;**176**:ITC97–ITC112. https://doi.org/10.7326/AITC202307180
2. Rivard L, Friberg L, Conen D, Healey JS, Berge T, Boriani G, *et al.* Atrial fibrillation and dementia: a report from the AF-SCREEN international collaboration. *Circulation* 2022;**145**:392–409. https://doi.org/10.1161/CIRCULATIONAHA.121.055018
3. Koh YH, Lew LZW, Franke KB, Elliott AD, Lau DH, Thiyagarajah A, *et al.* Predictive role of atrial fibrillation in cognitive decline: a systematic review and meta-analysis of 2.8 million individuals. *Europace* 2022;**24**:1229–39. https://doi.org/10.1093/europace/euac003
4. Kogelschatz B, Zenger B, Steinberg BA, Ranjan R, Jared Bunch T. Atrial fibrillation and the risk of early-onset dementia and cognitive decline: an updated review. *Trends Cardiovasc Med* 2023;**34**:236–41. https://doi.org/10.1016/j.tcm.2023.01.005

5. Zhang W, Liang J, Li C, Gao D, Ma Q, Pan Y, *et al.* Age at diagnosis of atrial fibrillation and incident dementia. *JAMA Netw Open* 2023;**6**:e2342744. https://doi.org/10.1001/jamanetworkopen.2023.42744
6. Nakase T, Tatewaki Y, Thyreau B, Odagiri H, Tomita N, Yamamoto S, *et al.* Impact of atrial fibrillation on the cognitive decline in Alzheimer's disease. *Alzheimers Res Ther* 2023;**15**:15. https://doi.org/10.1186/s13195-023-01165-1
7. Klostranec JM, Vucevic D, Bhatia KD, Kortman HGJ, Krings T, Murphy KP, *et al.* Current concepts in intracranial interstitial fluid transport and the glymphatic system: part I-anatomy and physiology. *Radiology* 2021;**301**:502–14. https://doi.org/10.1148/radiol.2021202043
8. Siow TY, Toh CH, Hsu JL, Liu GH, Lee SH, Chen NH, *et al.* Association of sleep, neuropsychological performance, and gray matter volume with glymphatic function in community-dwelling older adults. *Neurology* 2022;**98**:e829–38. https://doi.org/10.1212/WNL.0000000000013215
9. Hsu JL, Wei YC, Toh CH, Hsiao IT, Lin KJ, Yen TC, *et al.* Magnetic resonance images implicate that glymphatic alterations mediate cognitive dysfunction in Alzheimer disease. *Ann Neurol* 2023;**93**:164–74. https://doi.org/10.1002/ana.26516
10. Kamagata K, Andica C, Takabayashi K, Saito Y, Taoka T, Nozaki H, *et al.* Association of MRI indices of glymphatic system with amyloid deposition and cognition in mild cognitive impairment and Alzheimer disease. *Neurology* 2022;**99**:e2648–60. https://doi.org/10.1212/WNL.0000000000201300
11. Nedergaard M, Goldman SA. Glymphatic failure as a final common pathway to dementia. *Science* 2020;**370**:50–6. https://doi.org/10.1126/science.abb8739
12. Mestre H, Tithof J, Du T, Song W, Peng W, Sweeney AM, *et al.* Flow of cerebrospinal fluid is driven by arterial pulsations and is reduced in hypertension. *Nat Commun* 2018;**9**:4878. https://doi.org/10.1038/s41467-018-07318-3
13. Rajna Z, Mattila H, Huotari N, Tuovinen T, Kruger J, Holst SC, *et al.* Cardiovascular brain impulses in Alzheimer's disease. *Brain* 2021;**144**:2214–26. https://doi.org/10.1093/brain/awab144
14. Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM, *et al.* 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation* 2024;**149**:e1–156. https://doi.org/10.1161/CIR.0000000000001193
15. Bae YJ, Kim JM, Choi BS, Ryoo N, Song YS, Nam Y, *et al.* Altered brain glymphatic flow at diffusion-tensor MRI in rapid eye movement sleep behavior disorder. *Radiology* 2023;**307**:e221848. https://doi.org/10.1148/radiol.221848
16. Taoka T, Masutani Y, Kawai H, Nakane T, Matsuoka K, Yasuno F, *et al.* Evaluation of glymphatic system activity with the diffusion MR technique: diffusion tensor image analysis along the perivascular space (DTI-ALPS) in Alzheimer's disease cases. *Jpn J Radiol* 2017;**35**:172–8. https://doi.org/10.1007/s11604-017-0617-z
17. Jiang D, Liu L, Kong Y, Chen Z, Rosa-Neto P, Chen K, *et al.* Regional glymphatic abnormality in behavioral variant frontotemporal dementia. *Ann Neurol* 2023;**94**:442–56. https://doi.org/10.1002/ana.26710
18. Liu S, Sun X, Ren Q, Chen Y, Dai T, Yang Y, *et al.* Glymphatic dysfunction in patients with early-stage amyotrophic lateral sclerosis. *Brain* 2024;**147**:100–8. https://doi.org/10.1093/brain/awad274
19. Liu X, Barisano G, Shao X, Jann K, Ringman JM, Lu H, *et al.* Cross-vendor test-retest validation of diffusion tensor image analysis along the perivascular space (DTI-ALPS) for evaluating glymphatic system function. *Aging Dis* 2024;**15**:1885–98. https://doi.org/10.14336/AD.2023.0321-2
20. Blum S, Conen D. Mechanisms and clinical manifestations of cognitive decline in atrial fibrillation patients: potential implications for preventing dementia. *Can J Cardiol* 2023;**39**:159–71. https://doi.org/10.1016/j.cjca.2022.10.013
21. Madhavan M, Graff-Radford J, Piccini JP, Gersh BJ. Cognitive dysfunction in atrial fibrillation. *Nat Rev Cardiol* 2018;**15**:744–56. https://doi.org/10.1038/s41569-018-0075-z
22. Islam MM, Poly TN, Walther BA, Yang HC, Wu CC, Lin MC, *et al.* Association between atrial fibrillation and dementia: a meta-analysis. *Front Aging Neurosci* 2019;**11**:305. https://doi.org/10.3389/fnagi.2019.00305
23. Knecht S, Oelschlager C, Duning T, Lohmann H, Albers J, Stehling C, *et al.* Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy. *Eur Heart J* 2008;**29**:2125–32. https://doi.org/10.1093/eurheartj/ehn341
24. Berman JP, Norby FL, Mosley T, Soliman EZ, Gottesman RF, Lutsey PL, *et al.* Atrial fibrillation and brain magnetic resonance imaging abnormalities. *Stroke* 2019;**50**:783–8. https://doi.org/10.1161/STROKEAHA.118.024143
25. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, *et al.* Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* 2020;**396**:413–46. https://doi.org/10.1016/S0140-6736(20)30367-6
26. Kress BT, Iliff JJ, Xia M, Wang M, Wei HS, Zeppenfeld D, *et al.* Impairment of paravascular clearance pathways in the aging brain. *Ann Neurol* 2014;**76**:845–61. https://doi.org/10.1002/ana.24271
27. Ishida K, Yamada K, Nishiyama R, Hashimoto T, Nishida I, Abe Y, *et al.* Glymphatic system clears extracellular tau and protects from tau aggregation and neurodegeneration. *J Exp Med* 2022;**219**:e20211275. https://doi.org/10.1084/jem.20211275.
28. Harrison IF, Siow B, Akilo AB, Evans PG, Ismail O, Ohene Y, *et al.* Non-invasive imaging of CSF-mediated brain clearance pathways via assessment of perivascular fluid movement with diffusion tensor MRI. *Elife* 2018;**7**:e34028. https://doi.org/10.7554/eLife.34028
29. Saglietto A, Scarsoglio S, Tripoli F, Zwanenburg J, Biessels GJ, De Ferrari GM, *et al.* Atrial fibrillation hemodynamic effects on lenticulostriate arteries identified at 7-Tesla cerebral magnetic resonance imaging. *Clin Transl Med* 2023;**13**:e1367. https://doi.org/10.1002/ctm2.1367
30. Saglietto A, Scarsoglio S, Canova D, Roatta S, Gianotto N, Piccotti A, *et al.* Increased beat-to-beat variability of cerebral microcirculatory perfusion during atrial fibrillation: a near-infrared spectroscopy study. *Europace* 2021;**23**:1219–26. https://doi.org/10.1093/europace/euab070
31. Li S, Pei H, Huang Y, Liu D, Yang L, Zhang Q, *et al.* Experimental study on the effect of chlorhexidine gluconate (CG)-induced atrial fibrillation on renal water and sodium metabolism. *Sci Rep* 2023;**13**:4016. https://doi.org/10.1038/s41598-023-30783-w
32. Cheng Y, Chao J, Dai D, Dai Y, Zhu D, Liu B. AQP4-knockout aggravation of isoprenaline-induced myocardial injury is mediated by p66Shc and endoplasmic reticulum stress. *Clin Exp Pharmacol Physiol* 2017;**44**:1106–15. https://doi.org/10.1111/1440-1681.12812
33. Staerk L, Sherer JA, Ko D, Benjamin EJ, Helm RH. Atrial fibrillation: epidemiology, pathophysiology, and clinical outcomes. *Circ Res* 2017;**120**:1501–17. https://doi.org/10.1161/CIRCRESAHA.117.309732
34. Grymonprez M, Petrovic M, De Backer TL, Ikram MA, Steurbaut S, Lahousse L. Comparing the risk of dementia in subjects with atrial fibrillation using non-vitamin K antagonist oral anticoagulants versus vitamin K antagonists: a Belgian nationwide cohort study. *Age Ageing* 2023;**52**:afad038. https://doi.org/10.1093/ageing/afad038
35. Moffitt P, Lane DA, Park H, O'Connell J, Quinn TJ. Thromboprophylaxis in atrial fibrillation and association with cognitive decline: systematic review. *Age Ageing* 2016;**45**:767–75. https://doi.org/10.1093/ageing/afw104
36. Lin M, Han W, Zhong J, Wu L. A systematic review and meta-analysis to determine the effect of oral anticoagulants on incidence of dementia in patients with atrial fibrillation. *Int J Clin Pract* 2021;**75**:e14269. https://doi.org/10.1111/ijcp.14269
37. Guo J, Liu Y, Jia J, Lu J, Wang D, Zhang J, *et al.* Effects of rhythm-control and rate-control strategies on cognitive function and dementia in atrial fibrillation: a systematic review and meta-analysis. *Age Ageing* 2024;**53**:afae009. https://doi.org/10.1093/ageing/afae009
38. Writing Committee Members; Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, *et al.* 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *J Am Coll Cardiol* 2024;**83**:109–279. https://doi.org/10.1016/j.jacc.2023.08.017
39. Zhang W, Zhou Y, Wang J, Gong X, Chen Z, Zhang X, *et al.* Glymphatic clearance function in patients with cerebral small vessel disease. *Neuroimage* 2021;**238**:118257. https://doi.org/10.1016/j.neuroimage.2021.118257
40. Bae YJ, Choi BS, Kim JM, Choi JH, Cho SJ, Kim JH. Altered glymphatic system in idiopathic normal pressure hydrocephalus. *Parkinsonism Relat Disord* 2021;**82**:56–60. https://doi.org/10.1016/j.parkreldis.2020.11.009