Cerebral Microbleeds With Atrial Fibrillation After Ablation Therapy

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Research Article

Keywords: cerebral microbleeds, atrial fibrillation, cerebral infarction

Posted Date: September 29th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-924427/v1>

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Version of Record: A version of this preprint was published at Frontiers in Cellular Neuroscience on February 14th, 2022. See the published version at <https://doi.org/10.3389/fncel.2022.818288>.

Abstract

Background: The prevalence of cerebral microbleeds (CMBs) is significantly higher in patients with atrial fibrillation (AF) than in those without AF. CMBs in patients with AF have been reported to be primarily of the lobar type, but the exact cause of this remains unknown. We investigated the possibility that hemorrhagic transformation of embolic microinfarction can account for *de novo* lobar CMBs.

Methods: A total of 101 patients who underwent ablation therapy for AF were prospectively registered, and 72 patients completed the assessment with MRI 6 months after catheter ablation. Brain MRI, including diffusion-weighted imaging (DWI) and susceptibility-weighted imaging (SWI), were examined at 1–3 days (baseline) and 6 months after catheter ablation. We quantitatively evaluated the spatial and temporal distribution of embolic microinfarctions and *de novo* CMBs.

Results: Of the 101 patients, 68 were enrolled in this study. Fifty-nine patients (86.8%) showed embolic microinfarctions on baseline DWI immediately after catheter ablation. There were 137 CMBs in SWI, and 96 CMBs were of the lobar type. Six months later, there were 208 CMBs, including 71 *de novo* CMBs, and 60 of 71 (84.5%) were of the lobar type. Of the 71 *de novo* CMBs, 56 (78.9%) corresponded exactly to the location of previous embolic microinfarctions found on baseline DWI. The platelet count was significantly lower and hematocrit/hemoglobin and Fazekas score were higher in the group with *de novo* CMBs than in the group without *de novo* CMBs.

Conclusions: *De novo* CMBs frequently appeared after catheter ablation therapy. Our results suggest that embolic microinfarction can cause lobar CMBs.

Introduction

Cerebral microbleeds (CMBs) are small perivascular accumulations of hemosiderin-containing macrophages as a result of extravasation of erythrocytes from cerebral small vessels on histopathological examinations. In neuroimaging, CMBs are defined as small hypointense foci < 10 mm in diameter on magnetic resonance imaging (MRI) using T2*-weighted gradient-recalled echo or susceptibility-weighted imaging (SWI)^{1,2,3}. CMBs are classified into two types according to their location (deep and lobar CMBs), and histopathological analysis reveals mainly two types of vascular pathological changes, hypertensive vasculopathy and cerebral amyloid angiopathy (CAA), respectively. Strictly, the lobar CMBs are mostly considered to be caused by CAA and are found frequently in patients with Alzheimer's disease^{4,5}, whereas the non-lobar, deep or infratentorial, and mixed types of CMBs are considered to be due to hypertensive vasculopathy³.

Atrial fibrillation (AF) is a common arrhythmia, and its prevalence is increasing worldwide⁶. AF is associated not only with ischemic stroke, but also dementia. AF and dementia share multiple risk factors, and a meta-analysis study has revealed that there is an increased risk of dementia either with or without stroke⁷. One plausible cause of dementia with AF is the presence of cerebral infarctions⁸ and the other

mechanism may be the existence of CMBs which have been suggested to be associated with cognitive dysfunction⁹.

The prevalence of CMBs is significantly higher in patients with AF than in those without AF^{4, 10, 11}, and CMBs in patients with AF have been reported to be primarily of the lobar type^{4, 12}. The underlying pathophysiology of strictly lobar CMBs in patients with AF is yet to be ascertained⁴. In a previous study, we have reported alleviation of cognitive dysfunction after performing catheter ablation in patients with AF¹³, and observed *de novo* appearance of CMBs in correspondence with preexisting embolic microinfarctions. To investigate the possibility that hemorrhagic transformation of embolic microinfarction can account for *de novo* CMBs in patients with AF, we quantitatively investigated the association between embolic microinfarctions and CMBs on brain MRI.

Patients And Methods

Study protocol

This prospective study was approved by the ethical review board of Mie University Hospital (certificate number 3,038), and all patients provided written informed consent. All methods were performed in accordance with the Declaration of Helsinki. All patients were recruited from the Department of Cardiology, Mie University Hospital between August 2018 and September 2019. We recruited 101 patients who were admitted to the hospital for AF catheter ablation¹³.

We obtained clinical information, laboratory, and imaging data at baseline and follow-up after catheter ablation. Detailed clinical information, including age; sex; height; weight; blood pressure; heart rate; medical history, such as hypertension, hyperlipidemia, and diabetes mellitus; history of transient ischemic attack and/or stroke; and medication at baseline, was collected.

Ablation procedure

Catheter ablation was performed as described previously¹⁴. After obtaining informed consent, an electrophysiological study was performed in the post-absorptive state under light sedation. After internal jugular and femoral vein punctures, a heparin bolus (100 U/kg) was administered, and continuous infusion of heparin was provided thereafter to maintain an activated clotting time between 250 and 350 s. A diagnostic duodecapolar catheter was placed in the coronary sinus via the jugular vein. Three long sheaths were inserted through the femoral vein and introduced into the left atrium (LA) through a single trans septal puncture guided by intracardiac echocardiography. An eicosapolar circumferential catheter (Lasso 2515, Biosense Webster, Diamond Bar, CA, USA) and a multispline mapping catheter (PentaRay, Biosense Webster) were introduced into the LA through the trans septal long sheaths.

All imaging was performed using a biplane flat panel detector angiographic suite (Allura Xper FD10/10 Angio system; Philips Healthcare, Best, the Netherlands). Electroanatomical mapping was performed using the CARTO3 mapping system (Biosense Webster). Radiofrequency ablation was performed with an

irrigated catheter (EZ Steer Thermocool, Biosense Webster) using 0.9% normal saline and a point-by-point technique. Extensive encircling pulmonary vein isolation (EPPVI) was performed in patients with paroxysmal AF, and entrance and exit blocks were documented in all patients using Lasso2515 and PentaRay multipolar catheters. In addition to EPPVI, patients with persistent AF received LA posterior wall isolation. Additional linear ablation was performed along the LA roof to connect the left superior pulmonary vein to the right superior pulmonary vein and linear ablation along the LA floor to connect the inferior margin of the left inferior pulmonary vein to the right inferior pulmonary vein to obtain a block into the posterior wall. A bidirectional block was confirmed across all linear ablations using differential pacing techniques. If common atrial flutter was induced by atrial tachycardia pacing, cavotricuspid isthmus line ablation was performed in patients with paroxysmal AF and persistent AF.

Magnetic resonance imaging (MRI) protocol

MRI studies were performed at 1 to 3 days (baseline) and 6 months after ablation (follow-up) with a 3T MR unit (Ingenia, Philips Medical System, The Netherlands) using a 32-channel phased-array head coil¹³. We used diffusion-weighted imaging (DWI), three-dimensional (3D) fluid-attenuated inversion recovery (3D-FLAIR), 3D double inversion recovery (3D-DIR), and 3D T1-weighted imaging (3D-T1WI) to detect microemboli^{15, 16}. Acute microinfarctions were diagnosed using DWI images, whereas chronic microinfarctions were evaluated using 3D-DIR, 3D-FLAIR, and 3D-T1WI images. SWI was used to detect CMBs.

3D-DIR parameters were as follows: FOV, 250 mm; matrix, 208 × 163; thickness, 1.3 mm; TR (ms)/TE (ms), 5,500/247; TI (ms), 2,550/450; NEX, 2; and acquisition time, 5 min 13 s.

3D-FLAIR parameters were as follows: FOV, 250 mm; matrix, 256 × 184; thickness, 1.14 mm; TR (ms)/TE (ms), 6,000/390; TI, 2,000 ms; NEX, 2; and acquisition time, 4 min 42 s.

3D-T1WI imaging used turbo-field echo sequence and the following parameters: FOV, 260 mm; matrix, 288 × 288; thickness, 0.9 mm; TR (ms)/TE (ms), 8.4/4.7; NEX, 1; FA, 10°; and acquisition time, 4 min 56 s.

SWI parameters were as follows: FOV, 230 mm; matrix, 384 × 300; thickness, 2 mm; TR (ms)/TE (ms), 31/7.2; NEX, 1; FA, 17°; and acquisition time, 4 min 52 s.

And DWI parameters: FOV, 220 mm; matrix, 112 × 168; thickness, 3 mm without gap; TR (ms)/TE (ms), 5800 /87; b value = 1,000 s/mm²; NEX, 1; three orthogonal diffusion directions; and acquisition time, 1 min 10 s.

CMBs and cortical superficial siderosis, white matter hyperintensity (WMH) and lacunar infarcts, and acute microinfarctions were evaluated using SWI, 3D-FLAIR, and DWI, respectively¹⁷. Periventricular and deep WMHs were assessed according to the Fazekas rating scale¹⁸. MRI images were thoroughly analyzed by two trained neurologists (Y.H. and N.K.) who were blinded to the clinical data.

Statistical analysis

For the analyses of the differences in demographic characteristics, the Mann-Whitney U test and the χ -square test were used. To compare the difference in medical history between the group with newly detected *de novo* CMBs (positive group) and the group without *de novo* CMBs (negative group), the χ -square test was used. To compare the difference in DWI-positive lesions and Fazekas scores between the two groups, the Mann-Whitney U test was used. Statistical analyses were performed using the Statistical Package for the Social Sciences Statistics software version 27 (IBM Corporation, Armonk, NY, USA).

Results

Patient characteristics

A total of 101 patients underwent MRI 1 to 3 days after ablation. Six months after ablation, 72 patients underwent MRI, and 29 patients did not. Because of predetermined disqualification, four patients were excluded (Fig. 1): one with a history of ablation more than three times, and three with more than 50 CMBs.

The baseline characteristics of the patients are presented in Table 1. The median age at baseline was 69.0 ± 9.5 (range 32–86) years, and 49 patients were male (72.1%). All patients were administered oral anticoagulants. Moreover, 45 patients had hypertension (66.2%), nine had diabetes mellitus (13.2%), 28 had dyslipidemia (41.2%), and one had a history of stroke (1.5%). None of the patients had any neurological abnormality after ablation.

Table 1

Characteristics of the 68 patients with AF.

	All	De novo CMB-positive group (n= 35)	De novo CMB-negative group (n= 33)	<i>p</i> value
Mean age (years)	69.0 ± 9.5	67.7 ± 11.2	69.1 ± 7.4	0.980
Male sex, (n, %)	49 (72.1%)	25 (71.4%)	24 (72.7%)	0.560
Height (cm)	164.1 ± 9.2	162.8 ± 9.0	165.4 ± 9.4	0.269
Weight (kg)	65.8 ± 15.0	65.9 ± 17.5	65.7 ± 12.2	0.645
Body mass index (kg/m ²)	24.3 ± 4.6	24.3 ± 5.1	24.0 ± 4.0	0.754
Current smoking (n, %)	34 (50.0%)	14 (40.0%)	20 (60.6%)	0.072
Blood pressure and Heart rate				
Systolic blood pressure (mmHg)	132.8 ± 19.5	130.9 ± 20.2	134.8 ± 18.8	0.348
Diastolic blood pressure (mmHg)	77.9 ± 12.8	77.8 ± 11.9	77.9 ± 13.7	0.839
Heart rate (beat per minute)	71.9 ± 13.9	70.6 ± 13.9	73.4 ± 13.9	0.418
Past history				
Hypertension (n, %)	45 (66.2%)	22 (62.9%)	23 (69.7%)	0.368
Dyslipidemia (n, %)	28 (41.2%)	13 (37.1%)	15 (45.5%)	0.327
Diabetes mellitus (n, %)	9 (13.2%)	5 (14.2%)	4 (12.1%)	0.539
history of TIA and/or stroke (n, %)	1 (1.5%)	1 (2.8%)	0 (0%)	0.515
Medication				
antiplatelet (n, %)	9 (13.2%)	6 (17.1%)	3 (9.1%)	0.269
statin (n, %)	24 (35.2%)	12 (34.2%)	12 (36.4%)	0.529

Brain MRI findings 6 months after ablation

Figures 2 and 3 show two representative patterns of MRI findings. At baseline, DWI detected embolic microinfarcts in 59 out of 68 patients (86.8%), with a total of 392 lesions. These embolic microinfarcts were classified as the lobar (346), deep (11), and infratentorial lesions (35). CMBs were observed in 59 out of 68 patients (86.8%), with a total of 137 lesions on SWI at baseline. These CMBs were in the lobar (96), deep (19), and infratentorial areas (22). Six months later, MRI detected 208 CMBs with SWI. These were in the lobar (156), deep (24), and infratentorial (28) areas. Consequently, 71 *de novo* CMBs were revealed. They were in the lobar (60), deep (5), and infratentorial (6) areas. Additionally, 56 out of 71 *de novo* CMBs (78.9%) were located in exactly the same location as where embolic microinfarctions were found at baseline MRI (Fig. 2, Table 2).

Table 2
Number of embolic microinfarctions and CMBs at baseline and after 6 months.

	total	lobar	deep	infratentorial
embolic microinfarctions (baseline)	392	346 (88.3%)	11 (2.8%)	35 (8.9%)
CMBs (baseline)	137	96 (70.1%)	19 (13.9%)	22 (16.1%)
CMBs(after 6 months)	208	156 (75.0%)	24 (11.5%)	28 (13.5%)
<i>de novo</i> CMBs	71	60 (84.5%)	5 (7.0%)	6 (8.5%)
CMBs due to microinfarct	56	51 (91.1%)	1 (1.8%)	4 (7.1%)
CMBs without relation to microinfarct	15	9 (60.0%)	4 (26.7%)	2 (13.3%)
Abbreviations: AF, atrial fibrillation; CMBs, cerebral microbleeds; DWMH, deep white matter hyperintensity; PVH, periventricular hyperintensity				

Imaging and laboratory characteristics of patients between the *de novo* CMB-positive and *de novo* CMB-negative groups are also shown in Tables 3. When we compared the positive and negative groups for *de novo* CMBs, DWI-positive lesions at baseline, especially those in the lobar area, were significantly higher in the positive group ($P = .01$). Furthermore, the Fazekas scores for both periventricular hyperintensity and deep white matter hyperintensity were significantly higher in the positive group than in the negative group ($P < .05$). Moreover, hemoglobin and hematocrit levels were significantly higher in the positive group than in the negative group ($P < .05$), and platelet count was significantly lower in the positive group than in the negative group ($P < .01$).

Table 3
MRI findings, laboratory and echocardiography findings in the 68 patients with AF.

	All	de novo CMB-positive group (n = 35)	de novo CMB-negative group (n = 33)	p value
MRI findings				
Embololic microinfarctions(baseline)				
Total	5.8 ± 6.9	8.1 ± 8.1	3.2 ± 4.4	0.01*
Lobar	5.1 ± 6.2	7.0 ± 7.2	3.0 ± 4.3	0.01*
Deep	0.2 ± 0.5	0.3 ± 0.6	0.1 ± 0.2	0.089
Infratentorial	0.5 ± 0.9	0.9 ± 1.1	0.2 ± 0.4	0.01*
PVH(Fazekas grade)	1.1 ± 0.9	1.3 ± 0.8	0.9 ± 0.8	0.024*
DWMH (Fazekas grade)	1.8 ± 0.9	2.1 ± 0.87	1.6 ± 0.9	0.041*
CMBs (baseline)				
Total	2.0 ± 2.3	1.9 ± 1.9	2.2 ± 2.7	0.96
Lobar	1.4 ± 1.7	1.4 ± 1.6	1.4 ± 1.8	0.63
Deep	0.3 ± 0.7	0.2 ± 0.5	0.3 ± 0.9	0.91
Infratentorial	0.3 ± 0.7	0.2 ± 0.6	0.4 ± 0.7	0.21
6 months				
Total	3.1 ± 2.7	3.9 ± 2.4	2.2 ± 2.7	0.01*
Lobar	2.3 ± 2.1	3.1 ± 2.1	1.4 ± 1.8	0.01*
Deep	0.4 ± 0.9	0.4 ± 0.8	0.3 ± 0.9	0.49
Infratentorial	0.4 ± 0.7	0.4 ± 0.7	0.4 ± 0.7	0.92
Cortical superficial siderosis (n)	1 (1.0%)	1 (0.3%)	0	0.52
Lacune	0.9 ± 2.0	0.8 ± 2.2	1.0 ± 1.9	0.60
Enlargement of perivascular spaces	51 (75.0%)	28 (80.0%)	23 (70.0%)	0.24

Abbreviations: AF, atrial fibrillation; CMBs, cerebral microbleeds; DWMH, deep white matter hyperintensity; PVH, periventricular hyperintensity; WBC, white blood cell ; RBC, red blood cell ; APTT, activated partial thromboplastin time; PT, prothrombin time : PT-INR, prothrombin time-international normalized ratio; BNP, brain natriuretic peptide; SV, stroke volume; LAD, left atrial dimension; LAVI, left atrial volume index;

	All	de novo CMB-positive group (n = 35)	de novo CMB-negative group (n = 33)	p value
Centrum semiovale	12 (17.6%)	7 (20.0%)	5 (15.2%)	0.42
Basal ganglia	48 (70.6%)	26 (74.3%)	22 (66.7%)	0.34
Laboratory data				
WBC ($\times 10^3/\mu\text{L}$)	5.6 ± 1.7	5.4 ± 1.6	5.9 ± 1.7	0.141
RBC($\times 10^3/\mu\text{L}$)	445.0 ± 56.7	454.8 ± 63.5	434.6 ± 47.3	0.071
Hemoglobin (g/dl)	13.7 ± 1.6	14.1 ± 1.7	13.3 ± 1.4	0.026*
Hematocrit (%)	41.2 ± 4.6	42.4 ± 4.9	39.9 ± 4.1	0.023*
Platelet ($\times 10^3/\mu\text{L}$)	24.1 ± 18.2	19.8 ± 4.9	28.6 ± 25.1	0.003*
APTT(second)	36.9 ± 8.2	37.1 ± 7.0	36.8 ± 9.5	0.338
PT (%)	14.4 ± 3.2	14.8 ± 3.8	13.9 ± 2.5	0.397
PT-INR	1.2 ± 0.3	1.3 ± 0.4	1.2 ± 0.2	0.523
Fibrinogen (mg/dL)	271 ± 63.0	269.0 ± 63.6	274.3 ± 63.2	0.827
D-dimer ($\mu\text{g/mL}$)	0.6 ± 0.2	0.5 ± 0.01	0.62 ± 0.31	0.201
BNP (ng/mL)	82.8 ± 67.4	94.8 ± 70.5	70.0 ± 62.6	0.103
Echocardiography				
SV (ml)	67.8 ± 16.7	66.0 ± 16.1	69.6 ± 17.4	0.414
LAD (mm)	41.4 ± 7.1	42.2 ± 7.6	40.6 ± 6.4	0.601

Abbreviations: AF, atrial fibrillation; CMBs, cerebral microbleeds; DWMH, deep white matter hyperintensity; PVH, periventricular hyperintensity; WBC, white blood cell ; RBC, red blood cell ; APTT, activated partial thromboplastin time; PT, prothrombin time : PT-INR, prothrombin time-international normalized ratio; BNP, brain natriuretic peptide; SV, stroke volume; LAD, left atrial dimension; LAVI, left atrial volume index;

	All	de novo CMB-positive group (n = 35)	de novo CMB-negative group (n = 33)	p value
LAVI (ml/m ²)	46.3 ± 17.7	47.9 ± 17.7	44.7 ± 18.0	0.318
E/e'	11.4 ± 6.3	11.7 ± 8.1	11.0 ± 3.4	0.486
CHADS ₂ score	1.2 ± 1.0	1.2 ± 1.2	1.2 ± 0.8	0.555
HAS-BLED	1.2 ± 0.7	1.2 ± 0.6	1.2 ± 0.8	0.826
Abbreviations: AF, atrial fibrillation; CMBs, cerebral microbleeds; DWMH, deep white matter hyperintensity; PVH, periventricular hyperintensity; WBC, white blood cell ; RBC, red blood cell ; APTT, activated partial thromboplastin time; PT, prothrombin time : PT-INR, prothrombin time-international normalized ratio; BNP, brain natriuretic peptide; SV, stroke volume; LAD, left atrial dimension; LAVI, left atrial volume index;				

Discussion

In this study, we reported *de novo* CMBs in patients with AF after ablation therapy. First, *de novo* CMBs appeared in 35 (51.5%) patients 6 months after ablation therapy, and the location of almost 80% of *de novo* CMBs matched with the embolic microinfarctions detected on baseline MRI. Second, 84.5% of *de novo* CMBs were detected as the lobar type. Third, when comparing the positive and negative groups for *de novo* CMBs, the Fazekas score, and hemoglobin and hematocrit levels were higher in the positive group than in the negative group, while platelet count was significantly lower in the positive group than in the negative group.

This study revealed that *de novo* CMBs appeared after catheter ablation therapy, and most *de novo* CMBs were located spatially in correspondence to preceding embolic microinfarctions. Previous studies have reported a higher incidence of CMBs in patients with AF than in those without AF, and CMBs with AF were predominantly of the lobar type^{4, 11, 19}. Although anticoagulation therapy might be associated with the occurrence of CMBs^{20, 19}, the detailed pathogenesis of CMBs in patients with AF remains unclear. This study revealed a novel mechanism in that some *de novo* CMBs after catheter ablation were derived from embolic microinfarctions found at baseline MRI. Our previous study showed that small cortical infarctions could cause lobar CMBs, such as hemorrhagic transformation in ischemic stroke²¹. In accordance with these observation, a previous review has classified CMBs into either primary or secondary microbleeds²². Primary CMBs can be caused by the perivascular accumulation of hemosiderin-laden macrophages as a corollary of extravasated erythrocytes. Secondary CMBs may be caused by hemorrhagic transformation of microinfarction. Although our study evaluated only patients with AF after catheter ablation therapy, the present results may suggest that embolic CMBs could develop from incidentally-occurring microembolism and explain why CMBs in patients with AF are predominantly of the lobar type.

In the present study, the Fazekas score was higher in the positive group than in the negative group. Both periventricular and deep subcortical WMHs are often found on MRI in elderly people, and are a representative finding of cerebral small vessel disease²³. Periventricular and deep WMH are closely associated with CMBs²⁴. Moreover, another study has reported that CMBs are associated with recurrent stroke²⁵. Laboratory data in the present study revealed elevated hemoglobin and hematocrit values, and a decreased platelet count in the positive group compared to the negative group. A higher viscosity and fragility of hemostasis might be associated with microvascular disturbance, leading to development of CMBs.

Several studies have reported an association between AF and dementia^{7, 26, 27}. Although stroke events can increase the incidence of dementia, stroke-free patients with AF also have a higher risk of cognitive impairment and dementia^{7, 28}. The existence of more than three CMBs is reportedly associated with dementia²⁹, and, in reality, lobar CMBs are often observed in patients with AF^{4, 12}. Therefore, cognitive dysfunction in AF may be partially attributable to an increase in lobar CMBs. These CMBs may impair the functions of the cerebral cortex and cerebral white matter³⁰, since CMBs and cerebral microinfarcts are reportedly associated with cognitive dysfunction³¹. Recent studies have shown that treatment for AF, such as anticoagulants and ablation, can prevent cognitive decline^{32, 33, 34, 35}.

This study has some limitations. First, an MRI examination could not be performed before the ablation. Therefore, it cannot be denied that the CMBs at baseline MRI might have been affected by ablation therapy. Second, we could not compare the MRI findings of patients who underwent ablation therapy and those who did not. The incidence of CMBs in patients with AF in our study remains unclear. Moreover, we did not follow up the MRI images of patients with AF without ablation; it was not clear whether most patients with AF also had CMBs due to microinfarcts. A prospective study comparing patients with AF with and without ablation can resolve this problem. Therefore, further studies are required.

Conclusions

Our study showed that most *de novo* CMBs were derived from embolic microinfarctions and were of the lobar type after catheter ablation therapy in patients with AF. Some of the CMBs in patients with AF may have originated from incidental cerebral microinfarction.

References

1. Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Al-Shahi Salman R, Warach S, Launer LJ, Van Buchem MA, Breteler MM and Microbleed Study G. Cerebral microbleeds: a guide to detection and interpretation. *Lancet Neurol*. 2009;8:165-74.
2. Ogawa Ito A, Shindo A, Ii Y, Matsuura K, Tabei KI, Maeda M, Umino M, Suzuki Y, Shiba M, Toma N, Suzuki H and Tomimoto H. Microbleeds after Carotid Artery Stenting: Small Embolism May Induce Cerebral Microbleeds. *Cerebrovasc Dis Extra*. 2019;9:57-65.

3. Matsuyama H, li Y, Maeda M, Umino M, Ueda Y, Tabei KI, Kida H, Satoh M, Shindo A, Taniguchi A, Takahashi R and Tomimoto H. Background and distribution of lobar microbleeds in cognitive dysfunction. *Brain Behav.* 2017;7:e00856.
4. Selim M and Diener HC. Atrial Fibrillation and Microbleeds. *Stroke.* 2017;48:2660-2664.
5. Yates PA, Desmond PM, Phal PM, Steward C, Szoek C, Salvado O, Ellis KA, Martins RN, Masters CL, Ames D, Villemagne VL, Rowe CC and Group AR. Incidence of cerebral microbleeds in preclinical Alzheimer disease. *Neurology.* 2014;82:1266-73.
6. Bunch TJ. Atrial Fibrillation and Dementia. *Circulation.* 2020;142:618-620.
7. Kwok CS, Loke YK, Hale R, Potter JF and Myint PK. Atrial fibrillation and incidence of dementia: a systematic review and meta-analysis. *Neurology.* 2011;76:914-22.
8. Graff-Radford J, Madhavan M, Vemuri P, Rabinstein AA, Cha RH, Mielke MM, Kantarci K, Lowe V, Senjem ML, Gunter JL, Knopman DS, Petersen RC, Jack CR, Jr. and Roberts RO. Atrial fibrillation, cognitive impairment, and neuroimaging. *Alzheimers Dement.* 2016;12:391-8.
9. Poels MM, Ikram MA, van der Lugt A, Hofman A, Niessen WJ, Krestin GP, Breteler MM and Vernooij MW. Cerebral microbleeds are associated with worse cognitive function: the Rotterdam Scan Study. *Neurology.* 2012;78:326-33.
10. Saito T, Kawamura Y, Tanabe Y, Asanome A, Takahashi K, Sawada J, Katayama T, Sato N, Aizawa H and Hasebe N. Cerebral microbleeds and asymptomatic cerebral infarctions in patients with atrial fibrillation. *J Stroke Cerebrovasc Dis.* 2014;23:1616-22.
11. Horstmann S, Mohlenbruch M, Wegele C, Rizos T, Laible M, Rauch G and Veltkamp R. Prevalence of atrial fibrillation and association of previous antithrombotic treatment in patients with cerebral microbleeds. *Eur J Neurol.* 2015;22:1355-62.
12. Vernooij MW, Haag MD, van der Lugt A, Hofman A, Krestin GP, Stricker BH and Breteler MM. Use of antithrombotic drugs and the presence of cerebral microbleeds: the Rotterdam Scan Study. *Arch Neurol.* 2009;66:714-20.
13. Kato N, Muraga K, Hirata Y, Shindo A, Matsuura K, li Y, Shiga M, Tabei KI, Satoh M, Fujita S, Fukuma T, Kagawa Y, Fujii E, Umino M, Maeda M, Sakuma H, Ito M and Tomimoto H. Brain magnetic resonance imaging and cognitive alterations after ablation in patients with atrial fibrillation. *Sci Rep.* 2021;11:18995.
14. Sutter JS, Lokhnygina Y, Daubert JP, Bahnson T, Jackson K, Koontz JI, Sun AY, Hegland DD, Thomas KL, Jackson L, Lewis R, Granger C, Piccini JP and Atwater BD. Safety and efficacy outcomes of left atrial posterior wall isolation compared to pulmonary vein isolation and pulmonary vein isolation with linear ablation for the treatment of persistent atrial fibrillation. *Am Heart J.* 2020;220:89-96.
15. li Y, Maeda M, Kida H, Matsuo K, Shindo A, Taniguchi A and Tomimoto H. In vivo detection of cortical microinfarcts on ultrahigh-field MRI. *Journal of neuroimaging : official journal of the American Society of Neuroimaging.* 2013;23:28-32.
16. li Y, Maeda M, Ishikawa H, Ito A, Matsuo K, Umino M, Shindo A, Kida H, Satoh M, Niwa A, Taniguchi A and Tomimoto H. Cortical microinfarcts in patients with multiple lobar microbleeds on 3 T MRI.

Journal of neurology. 2019;266:1887-1896.

17. Charidimou A, Boulouis G, Gurol ME, Ayata C, Bacskai BJ, Frosch MP, Viswanathan A and Greenberg SM. Emerging concepts in sporadic cerebral amyloid angiopathy. *Brain.* 2017;140:1829-1850.
18. Fazekas F, Chawluk JB, Alavi A, Hurtig HI and Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol.* 1987;149:351-6.
19. Herm J, Schurig J, Martinek MR, Hölting R, Schirdewan A, Kirchhof P, Wiecek M, Pürerfellner H, Heuschmann PU, Fiebach JB and Haeusler KG. MRI-detected brain lesions in AF patients without further stroke risk factors undergoing ablation - a retrospective analysis of prospective studies. *BMC Cardiovasc Disord.* 2019;19:58.
20. Werring DJ, Frazer DW, Coward LJ, Losseff NA, Watt H, Cipolotti L, Brown MM and Jäger HR. Cognitive dysfunction in patients with cerebral microbleeds on T2*-weighted gradient-echo MRI. *Brain.* 2004;127:2265-75.
21. Ito AO, Shindo A, Li Y, Ishikawa H, Taniguchi A, Shiba M, Toma N, Suzuki H and Tomimoto H. Small Cortical Infarcts Transformed to Lobar Cerebral Microbleeds: A Case Series. *J Stroke Cerebrovasc Dis.* 2019;28:e30-e32.
22. Fisher M. Cerebral microbleeds: where are we now? *Neurology.* 2014;83:1304-5.
23. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley RI, O'Brien JT, Barkhof F, Benavente OR, Black SE, Brayne C, Breteler M, Chabriat H, DeCarli C, de Leeuw F-E, Doubal F, Duering M, Fox NC, Greenberg S, Hachinski V, Kilimann I, Mok V, Oostenbrugge Rv, Pantoni L, Speck O, Stephan BCM, Teipel S, Viswanathan A, Werring D, Chen C, Smith C, van Buchem M, Norrving B, Gorelick PB and Dichgans M. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *The Lancet Neurology.* 2013;12:822-838.
24. Yamada S, Saiki M, Satow T, Fukuda A, Ito M, Minami S and Miyamoto S. Periventricular and deep white matter leukoaraiosis have a closer association with cerebral microbleeds than age. *Eur J Neurol.* 2012;19:98-104.
25. Chatzikonstantinou A, Willmann O, Szabo K and Hennerici MG. Cerebral microbleeds are uncommon in ischemic stroke associated with nonvalvular atrial fibrillation. *J Neuroimaging.* 2011;21:103-7.
26. Bunch TJ, Weiss JP, Crandall BG, May HT, Bair TL, Osborn JS, Anderson JL, Muhlestein JB, Horne BD, Lappe DL and Day JD. Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. *Heart Rhythm.* 2010;7:433-7.
27. Ott A, Breteler MM, de Bruyne MC, van Harskamp F, Grobbee DE and Hofman A. Atrial fibrillation and dementia in a population-based study. The Rotterdam Study. *Stroke.* 1997;28:316-21.
28. Madhavan M, Graff-Radford J, Piccini JP and Gersh BJ. Cognitive dysfunction in atrial fibrillation. *Nat Rev Cardiol.* 2018;15:744-756.
29. Ding J, Sigurðsson S, Jónsson PV, Eiríksdóttir G, Meirelles O, Kjartansson O, Lopez OL, van Buchem MA, Gudnason V and Launer LJ. Space and location of cerebral microbleeds, cognitive decline, and dementia in the community. *Neurology.* 2017;88:2089-2097.

30. Werring DJ, Frazer DW, Coward LJ, Losseff NA, Watt H, Cipolotti L, Brown MM and Jager HR. Cognitive dysfunction in patients with cerebral microbleeds on T2*-weighted gradient-echo MRI. *Brain*. 2004;127:2265-75.
31. van Veluw SJ, Hilal S, Kuijf HJ, Ikram MK, Xin X, Yeow TB, Venketasubramanian N, Biessels GJ and Chen C. Cortical microinfarcts on 3T MRI: Clinical correlates in memory-clinic patients. *Alzheimers Dement*. 2015;11:1500-1509.
32. Jacobs V, May HT, Bair TL, Crandall BG, Cutler MJ, Day JD, Mallender C, Osborn JS, Stevens SM, Weiss JP, Woller SC and Bunch TJ. Long-Term Population-Based Cerebral Ischemic Event and Cognitive Outcomes of Direct Oral Anticoagulants Compared With Warfarin Among Long-term Anticoagulated Patients for Atrial Fibrillation. *Am J Cardiol*. 2016;118:210-4.
33. Friberg L and Rosenqvist M. Less dementia with oral anticoagulation in atrial fibrillation. *Eur Heart J*. 2018;39:453-460.
34. Bunch TJ, Crandall BG, Weiss JP, May HT, Bair TL, Osborn JS, Anderson JL, Muhlestein JB, Horne BD, Lappe DL and Day JD. Patients treated with catheter ablation for atrial fibrillation have long-term rates of death, stroke, and dementia similar to patients without atrial fibrillation. *J Cardiovasc Electrophysiol*. 2011;22:839-45.
35. Kim D, Yang PS, Sung JH, Jang E, Yu HT, Kim TH, Uhm JS, Kim JY, Pak HN, Lee MH, Lip GYH and Joung B. Less dementia after catheter ablation for atrial fibrillation: a nationwide cohort study. *Eur Heart J*. 2020;41:4483-4493.

Figures

Figure 1

Figure 1

Study protocol.

Figure 2

Figure 2

De novo cerebral microbleeds matched with microinfarcts. A 70-year-old woman showed an embolic microinfarct that was detected in the right occipital lobe on DWI (A) and 3D-DIR (B) at baseline, but no abnormality was found on SWI (C). After 6 months, DWI (D) and 3D-DIR (E) did not detect an abnormality. A de novo CMB was detected in the right occipital lobe by SWI(F), and the lesion was located in exactly the same location as where the embolic infarction was detected on baseline MRI.

Figure 3

Figure 3

De novo cerebral microbleeds mismatched with microinfarcts. A 75-year-old man showed no embolic microinfarct on DWI (A) or 3D-DIR (B), and no CMBs were found on SWI (C) at baseline. After 6 months, DWI (D) and 3D-DIR (E) did not detect any abnormalities. A de novo CMB was detected in the right frontal lobe by SWI (F) after 6 months, but the CMB was not related to microinfarction.