Risk factors and localization of silent cerebral infarction in patients with atrial fibrillation

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BACKGROUND It is important to identify the risk factors and localization of silent cerebral infarction (SCI), especially in younger patients with atrial fibrillation (AF).

OBJECTIVE The purpose of this study was to examine the characteristics and risk factors for SCI in AF patients, with particular attention to localization of SCI.

METHODS The study enrolled 286 consecutive neurologically asymptomatic patients who underwent AF ablation from January 2014 to July 2017 (age 61.7 ± 10.2 [SD] years; 208 male and 78 female). All patients underwent magnetic resonance imaging (MRI) before ablation.

RESULTS SCIs were classified independently by 2 radiologists as follows: cardiogenic SCI in 19 (10.6%), lacunar SCI in 13 (8.9%), undetermined causes in 6 (1.6%), and no SCI in 248 (controls, 78.7%). Importantly, no patients with CHA_2DS_2-VASc score 0 had SCI on MRI. In univariable analysis, significant risk factors for lacunar SCI included age ($P = .007$), hypertension ($P = .037$), congestive heart failure ($P = .040$), left atrial (LA) diameter ($P = .013$), and cardio-ankle vascular index ($P = .004$). In multivariable analysis, significant risk factors for cardiogenic SCI were AF duration (odds ratio [OR] 1.01; 95% confidence interval [CI] 1.00–1.02; $P = .038$), ankle-brachial pressure index (OR 0.002; 95% CI 0–0.68; $P = .030$), and LA abnormality (OR 8.99; 95% CI 2.78–31.00; $P < .001$), defined by the presence of spontaneous echo contrast and/or decreased LA appendage emptying velocity.

CONCLUSION The study results indicate that among AF patients, SCIs localized in the cerebral cortex and cerebellum are frequently noted, for which cardiogenic mechanisms may be mainly involved; CHA_2DS_2-VASc score could be useful for screening SCI; and LA abnormality is the specific marker for cardiogenic SCI, providing useful information for risk stratification of SCI.

KEYWORDS Atrial fibrillation; Cardiogenic cerebral embolism; Cardiogenic cerebral infarction; Risk stratification; Silent cerebral infarction

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Introduction

In several large population-based studies, silent cerebral infarction (SCI) was common in healthy people in whom small infarcts were mostly noted in the deep subcortical white matter in the absence of any clinically apparent neurological deficits or transient ischemic attack (TIA).[1,2] SCI is recognized as one of the important risk factors for cognitive decline, dementia,[3] and subsequent symptomatic stroke.[2,4] Previous systematic reviews identified advanced age, hypertension, diabetes mellitus, and smoking as risk factors for SCI in the general population.[1,2] Recent studies reported that the prevalence of SCI in patients with atrial fibrillation (AF) was significantly higher than in those without AF.[2,5,6] Thus, the 2017 American Heart Association/American Stroke Association (AHA/ASA) statement pointed out that risk stratification for SCI in AF patients is an important strategy for the prevention of dementia and symptomatic cerebral infarction in the future.[7]

Cardiogenic cerebral infarction, which is often caused by AF, has a poor prognosis because it causes broad and severe brain damage.[8] It also has a higher recurrence rate than other types of cerebral infarction.[9] A previous study identified risk factors for clinically symptomatic thromboembolism in patients with AF, including left atrial (LA) abnormalities (eg, LA thrombus, spontaneous echo contrast [SEC], and

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abnormal LA appendage emptying velocity (LAAeV]) and aortic abnormalities.[10] Moreover, recent studies have suggested that, in AF patients, microembolization of small thrombi from the fibrillating LA appendage (LAA) plays an important role in the occurrence of SCI.[11] Although the morphology and location of SCI could provide insight into the mechanisms underlying SCI formation, the characteristics and risk factors for SCI in AF patients remain to be fully elucidated. Thus, the present study was designed to examine the characteristics and risk factors for SCI in AF patients, with particular attention to localization of SCI.

Candidates for AF catheter ablation generally tend to be stratified as lower risk for symptomatic cerebral infarction because most of them are relatively younger and otherwise healthy, with relatively low $CHADS_2$ and CHA_2DS_2-VASc scores.[12] However, risk stratification for SCI in these patients would be important because subsequent symptomatic cerebral infarction would result in substantial social and economic burden; therefore, it would be beneficial to detect SCI accurately and to elucidate the treatable risk factors for this disorder. In the present study, we examined the risk factors and localization of SCI in candidates for AF catheter ablation.

Methods

The study protocol was approved by the Ethical Committee of Tohoku University (No. 2016-1-042), and all patients were informed of the study by posted information in our institute.

Study population

We retrospectively enrolled 286 consecutive patients who underwent their first AF catheter ablation in our hospital from January 2013 to December 2017 (age 61.7 ± 10.2 [SD] years; 208 male and 78 female). Each patient underwent brain magnetic resonance imaging (MRI) before catheter ablation. Exclusion criteria were patients with valvular AF, any mechanical prosthetic valve, or past history of symptomatic cerebral infarction.

Baseline evaluation

Patients were assessed based on medical history, routine blood tests, electrocardiogram, echocardiogram, and brain MRI. Medical history included hypertension, diabetes mellitus, congestive heart failure, coronary artery disease, peripheral artery disease, history of smoking, previous history of stroke or TIA, and previous use of antiplatelet or anticoagulation drugs. The $CHADS_2$ (Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, and prior Stroke or transient ischemic attack) score[13] and CHA_2DS_2-VASc (CHA_2DS_2 plus Vascular disease, Age 65-74 years, and female sex) score[14] were calculated for each patient. Transthoracic and transesophageal echocardiography were performed according to American Society of Echocardiography guidelines.[15] Ankle-brachial pressure index (ABI) and cardio-ankle vascular index (CAVI) were measured using an oscillometric device (VaSera VS-1500, Fukuda Denshi, Co Ltd, Tokyo, Japan) as described previously.[16]

Anticoagulant management

Direct oral anticoagulant (DOAC) or warfarin was administered at least 3 weeks before the ablation procedure. The choice of DOAC or warfarin was made by the attending physician. DOACs included apixaban, rivaroxaban, dabigatran, and edoxaban. Warfarin dosage was adjusted to maintain a target international normalized ratio of 2.0–3.0 (or 1.6–2.6 for patients ≥70 years old) according to consensus guidelines.[12] Duration without anticoagulation was defined as the time period from the diagnosis of AF to the start of anticoagulation.

Brain MRI

In order to completely and noninvasively detect SCI, we performed brain MRI, which was reported to be the most sensitive diagnostic method for the disorder.[17] All patients underwent brain MRI with a 1.5-T (n = 73, Achieva, Philips Medical Systems, Best, Netherlands; n = 44, Genesis Signa, GE Medical Systems, Milwaukee, Wisconsin) or 3-T MR unit (n = 68, Achieva 3 T, Philips Medical Systems, Best, Netherlands; n = 26, Ingenia 3.0T CX, Philips Medical Systems, Best, Netherlands; n = 38, Vantage Titan 3T, Toshiba Medical System, Otawara, Japan; n = 37, MAGNETOM Trio, A Tim System, Siemens Healthineers System, Erlangen, Germany) on the day before ablation. The imaging protocol included the following 4 pulse sequences, which were acquired in the axial plane through the anterior and posterior cerebral commissures: (1) diffusion-weighted image (DWI); (2) fluid-attenuated inversion recovery (FLAIR) image; (3) fast spin-echo T2-weighted spin-echo sequence image; and (4) spin-echo T1-weighted image in addition to magnetic resonance angiography (MRA). All diffusion-weighted images were performed in axial orientations. For image quality, it is important to choose the best fitting slice thickness for examination.[17] In the present study, slice thickness (6 mm) and gap (1 mm) were adjusted for screening.

We defined SCI as ≥1 cerebral infarctions on brain MRI, without a history of corresponding stroke or TIA. In order to include definite cerebral infarction and completely exclude lesions that might be mistaken for cerebral infarction, such as ischemic white matter hyperintensities, prominent perivascular space, and cerebral microbleeds, we defined cerebral infarctions as hypointense lesions that measured >3 mm on T1-weighted images and hyperintense lesions on T2-weighted images.[7] FLAIR images were used to separate dilated Virchow-Robin spaces from infarcts based on the absence or presence of a hyperintense rim around each of the suspected lesions.[17] Lesions lacking a hyperintense rim on FLAIR were considered to be dilated Virchow-Robin spaces. Hyperintensity lesions on DWI indicating acute ischemia were excluded.

All ischemic lesions were classified according to location as follows (Figure 1): noncortical infarcts, defined as focal, sharply demarcated noncortical lesions in the cerebral white matter or deep gray matter; cortical infarcts, defined as cortical lesions corresponding to the territories of large cerebral arteries; and cerebellar infarcts.[7] Ischemic lesions of the lower third of the basal ganglia were excluded because of the

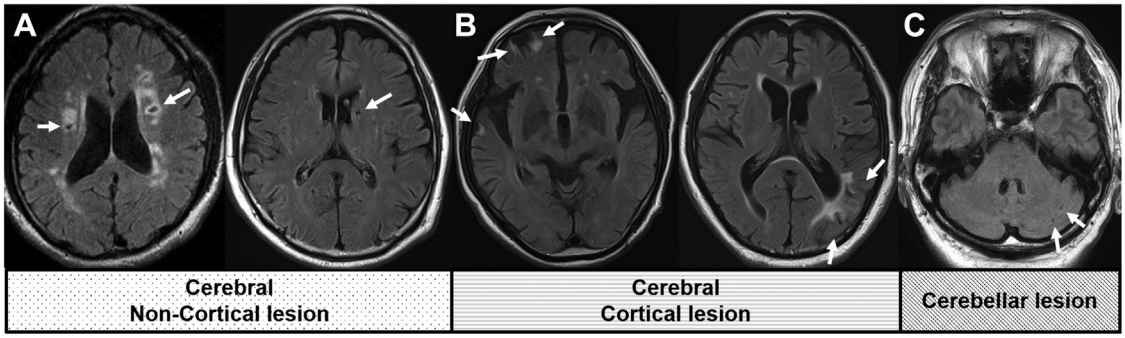


Figure 1 Classification of silent cerebral infarctions according to location on brain magnetic resonance imaging. **A:** Cerebral noncortical infarcts, defined as focal, sharply demarcated noncortical lesions in the cerebral white matter or deep gray matter. **B:** Cerebral cortical infarcts, defined as cortical lesions corresponding to the territories of large cerebral arteries. **C:** Cerebellar infarcts.

difficulty in distinguishing ischemic lesions from Virchow-Robin spaces.[17] Then, all ischemic lesions were diagnosed as follows: lacunar SCI, defined as relevant brainstem or subcortical hemispheric lesions with diameter <1.5 cm on FLAIR images; and cardiogenic SCI, defined as cortical lesions corresponding to the territories of large cerebral arteries without significant stenosis or occlusion of a major brain artery or branch cortical artery demonstrated on MRA. SCI with cortical lesions corresponding to the territories of large cerebral arteries with significant stenosis or occlusion of major brain artery or branch cortical artery demonstrated on MRA were excluded because they have ≥2 potential causes. MRI images were analyzed independently by 2 neuroradiologists who had not been informed of the clinical information, and conflict between them was resolved by common agreement.

Statistical analysis

Continuous data that were normally distributed are expressed as mean ± SD and were compared using the Student *t* test or 1-way analysis of variance with Tukey honestly significant different test for multiple comparisons. Categorical data are expressed as count (percentage) and were compared using the χ^2 test or Fisher exact test if needed. To identify the risk factors for cardiogenic and lacunar SCI, univariable logistic regression analysis was performed and then the backward stepwise selection method was used in the process of variable selection. Finally, those selected variables were included in a multivariable logistic regression model. $P < .05$ was considered significant. Analyses were performed using JMP 12 (SAS Institute Inc, Cary, NC).

Results

Clinical characteristics of patients with or without SCI

The clinical characteristics of the 286 patients are summarized in Table 1. Mean age was 61.7 ± 10.2 years, and 208 (72.4%) were male. The averaged value of risk scores for thromboembolic events was 0.9 ± 0.8 for $CHADS_2$ and 1.7 ± 1.2 for CHA_2DS_2-VASc. With regard to medications, all patients were treated with oral anticoagulants (258 [90.3%] with DOAC and 28 [9.7%] with warfarin), and 21 (7.3%) were treated with antiplatelet agents. Sixteen patients (57.1%) in the warfarin group were under the therapeutic range.

SCIs were detected in 38 of 286 patients (13.2%) on brain MRI (Figure 2). Of the 38 patients with SCI, 19 were diagnosed as having cardiogenic SCI and 13 lacunar SCI. Because the remaining 6 patients were considered to have ≥2 potential causes of SCI, the 2 neuroradiologists were unable to make a final diagnosis. Furthermore, it was noted that approximately half of SCI patients had multiple lesions (Figure 2). Although patients with $CHADS_2$ score of 0 showed SCI lesions on MRI, no patients with CHA_2DS_2-VASc score of 0 had SCI on MRI (Figure 3). Clinical characteristics of patients with CHA_2DS_2-VASc score 0 and ≥1 are given in Supplementary Table S1.

The clinical characteristics of patients with or without SCI are also listed in Table 1. Patients with SCI were older ($P = .014$); had a higher prevalence of nonparoxysmal AF ($P = .015$); and had higher $CHADS_2$ ($P < .001$) and CHA_2DS_2-VASc scores ($P < .001$), B-type natriuretic peptide (BNP) level ($P < .001$), and CAVI ($P = .004$) compared to patients without SCI. Patients with SCI had significantly larger LA diameter (LAD; 43.7 ± 6.5 mm vs 40.6 ± 6.2 mm; $P = .004$) and LA volume index (LAVI; 46.3 ± 16.8 ml/m^2 vs 38.9 ± 12.3 ml/m^2; $P = .001$); higher prevalence of LA abnormality (defined by the presence of SEC or decreased LAAeV; $P = .044$)[11]; and lower LAAeV (46.9 ± 20.0 cm/s vs 56.8 ± 22.2 cm/s; $P = .011$) than those without SCI.

Patient characteristics according to SCI subtypes

Clinical characteristics of patients with or without each subtype of SCI based on its location are listed in Table 1. Patients with cardiogenic SCI had significantly lower estimated glomerular filtration rate ($P = .003$); higher CHA_2DS_2-VASc scores ($P = .013$), BNP level ($P = .001$), and E/e′ ($P = .044$); and higher prevalence of SEC ($P = .029$) and LA abnormality ($P = .006$) than those without SCI. Patients with lacunar SCI had a significantly higher prevalence of congestive heart failure ($P = .042$), higher $CHADS_2$ ($P = .004$) and CHA_2DS_2-VASc scores ($P = .027$), and LAVI ($P = .024$) than those without SCI. Patients with

Table 1 Clinical characteristics of patients with or without SCI

	Total (n = 286)	Control (n = 248)	SCI (n = 38) Cardiogenic (n = 19)/lacunar (n = 13)	*P* value
General characteristics				
Age (y)	61.7 ± 10.2	61.0 ± 10.6	65.4 ± 6.6	.01
			65.0 ± 7.0/67.6 ± 6.1	.03
Male sex	208 (72.4)	178 (71.7)	30 (78.9)	.35
			12 (63.1)/12 (92.3)	.18
Body surface area (m^2)	1.7 ± 0.2	1.7 ± 0.2	1.7 ± 0.2	.20
			1.6 ± 0.2/1.7 ± 0.1	.34
Body mass index (kg/m^2)	24.4 ± 3.6	24.3 ± 3.7	24.3 ± 3.2	.99
			22.9 ± 3.1/24.9 ± 3.5	.39
Smoking habit	110 (38.3)	94 (37.9)	16 (42.1)	.74
			6 (31.5)/7 (53.8)	.53
AF duration (mo)	35.2 ± 47.3	34.8 ± 43.4	40.8 ± 50.0	.44
			56.8 ± .63.2/26.5 ± 22.1	.09
Duration with anticoagulation (mo)	11.6 ± 20.2	10.7 ± 18.6	17.6 ± 28.5	.067
			23.4 ± 36.2/10.2 ± 8.9	.037
Duration without anticoagulation (mo)	18.9 ± 37.7	18.1 ± 36.5	23.6 ± 44.9	.43
			34.9 ± 55.4/16.0 ± 21.0	.17
Symptomatic AF	228 (79.4)	199 (80.2)	29 (76.3)	.51
			15 (78.9)/10 (76.9)	.82
Nonparoxysmal AF	81 (28.2)	64 (25.8)	17 (44.7)	.02
			10 (52.6)/5 (38.4)	.03
eGFR ($mL/min/m^2$)	68.9 ± 16.7	69.9 ± 16.0	60.9 ± 19.6	.002
			56.6 ± 25.0/65.4 ± 8.6	.003
BNP (pg/mL)	69.3 ± 102.6	58.7 ± 79.5	124.2 ± 182.4	<.001
			148.0 ± 241.5/108.7 ± 104.7	<.001
Quantifying risk factors				
Age ≥75 y	21 (7.3)	17 (42.0)	4 (10.5)	.42
			2 (10.5)/2 (15.3)	.31
Age ≥65 y	133 (46.3)	113 (45.5)	20 (52.6)	.41
			9 (47.3)/9 (69.2)	.27
Congestive heart failure	25 (8.7)	17 (6.8)	8 (21.0)	.003
			4 (21.0)/4 (30.7)	.003
Diabetes mellitus	23 (8.0)	19 (7.6)	4 (10.5)	.54
			2 (10.5)/1 (7.6)	.75
Hypertension	162 (56.4)	133 (53.6)	29 (76.3)	.01
			14 (73.6)/11 (84.6)	.03
Coronary or vascular disease	25 (8.7)	18 (6.4)	7 (18.4)	.01
			4 (21.0)/2 (15.3)	.04
$CHADS_2$ score	0.9 ± 0.8	0.7 ± 0.6	1.1 ± 0.8	<.001
			1.1 ± 0.8/1.3 ± 0.8	.001
CHA_2DS_2-VASc score	1.7 ± 1.2	1.5 ± 1.1	2.2 ± 1.1	<.001
			2.3 ± 1.0/2.3 ± 1.3	.001
Medications				
Antiarrhythmic drug	163 (56.7)	140 (56.4)	23 (60.5)	.63
			12 (63.1)/7 (53.8)	.03
β-Blocker	134 (46.6)	109 (43.9)	25 (65.7)	.01
			12 (63.1)/11 (84.6)	.005
Calcium channel blocker	93 (32.4)	82 (33.0)	11 (28.9)	.61
			4 (21.0)/4 (30.7)	.62
Digitalis	12 (4.1)	8 (3.2)	4 (10.5)	.04
			2 (10.5)/1 (7.6)	.16
Antiplatelet drug	21 (7.3)	15 (6.0)	6 (15.7)	.03
			4 (21.0)/2 (15.3)	.03
DOAC	258 (90.2)	224 (90.3)	34 (89.4)	.68
			15 (78.9)/13 (100)	.13
Warfarin	28 (9.7)	24 (9.6)	4 (10.5)	.87
			4 (21.0)/0 (0)	.14
INR	1.9 ± 0.4	2.0 ± 0.3	1.2 ± 0.2	<.001
			1.2 ± 0.2/-	<.001
Under the therapeutic range	16 (57.1)	16 (66.6)	0 (0)	.14
			0(0)/-	.14

Table 1 (*Continued*)

	Total (n = 286)	Control (n = 248)	SCI (n = 38) Cardiogenic (n = 19)/lacunar (n = 13)	*P* value
Echocardiographic findings				
LVDd (mm)	47.4 ± 5.2	47.6 ± 5.1	46.3 ± 5.7	.17
			45.3 ± 5.2/47.3 ± 6.9	.19
LVDs (mm)	30.9 ± 5.4	31.0 ± 5.3	30.3 ± 6.3	.44
			30.1 ± 4.2/30.4 ± 9.1	.73
LAD (mm)	41.3 ± 6.3	40.6 ± 6.2	43.7 ± 6.5	.004
			42.6 ± 7.0/45.0 ± 5.4	.02
LAVI (ml/m^2)	40.6 ± 14.1	38.9 ± 12.3	46.3 ± 16.8	.002
			44.3 ± 16.3/49.5 ± 20.1	.01
LVEF (%)	63.5 ± 9.2	63.6 ± 9.1	61.9 ± 9.2	.27
			62.6 ± 6.2/61.9 ± 9.2	.26
E/e ′	10.4 ± 3.3	10.2 ± 3.3	11.2 ± 3.8	.48
			12.1 ± 4.4/9.6 ± 2.6	.04
SEC	38 (14.0)	29 (13.2)	9 (23.6)	.04
			7 (36.8)/1 (7.6)	.02
LAAeV (cm/s)	54.7 ± 22.3	56.8 ± 22.2	46.9 ± 20.0	.01
			45.0 ± 21.5/49.2 ± 20.5	.05
LA abnormality	39 (13.6)	30 (12.0)	9 (23.6)	.054
			7 (36.8)/1 (7.6)	.004
Atherosclerotic parameters				
CAVI	8.3 ± 1.2	8.2 ± 1.1	8.8 ± 1.3	.004
			8.6 ± 1.6/9.0 ± 0.7	.04
ABI	1.07 ± 0.09	1.07 ± 0.08	1.04 ± 0.13	.03
			1.04 ± 0.08/1.08 ± 0.15	.19

Values are given as mean ± SD or n (%) unless otherwise indicated.

ABI = ankle brachial pressure index; AF = atrial fibrillation; BNP = B-type natriuretic peptide; CAVI = cardio-ankle vascular index; DOAC = direct oral anticoagulant; eGFR = estimated glomerular filtration rate; LAAeV = left atrial appendage emptying velocity; LAD = left atrial diameter; LAVI = left atrial volume index; LVDd = left ventricular diastolic diameter; LVDs = left ventricular systolic diameter; LVEF = left ventricular ejection fraction; INR = international normalized ratio; SCI = silent cerebral infarction; SEC = spontaneous echo contrast.

cardiogenic SCI tended to have a higher prevalence of LA abnormality (P = .099) than those with lacunar SCI.

Risk factors for each subtype of SCI

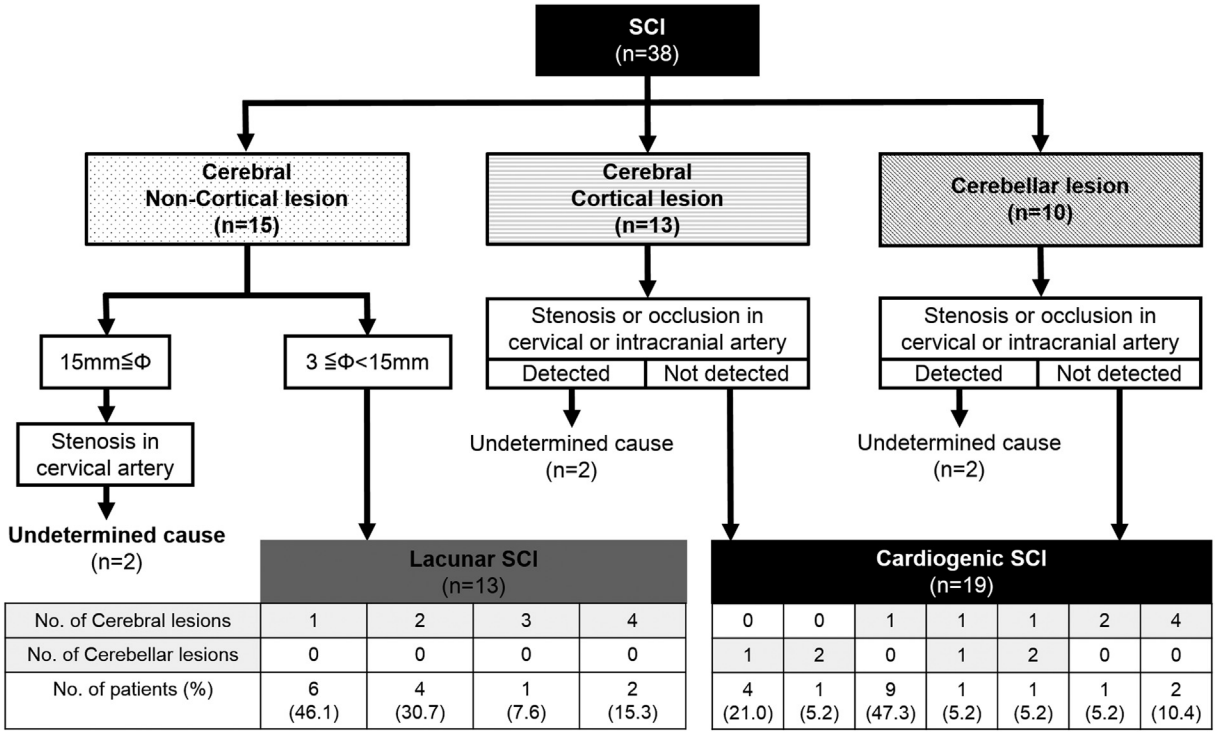
We performed univariable and multivariable analyses to identify the risk factors for cardiogenic SCI (Table 2). In univariable analysis, significant risk factors for cardiogenic SCI were AF duration (P = .043), nonparoxysmal AF (P = .019), coronary/vascular disease (P = .037), estimated glomerular filtration rate (P = .002), BNP level (P = .004), E/e ′ (P = .018), LA abnormality (P = .001), and ABI (P = .072). Furthermore, multivariable analysis revealed that LA abnormality (odds ratio [OR] 8.99; 95% confidence interval [CI] 2.78–31.00; P <.001), AF duration (OR 1.01; 95% CI 1.00–1.02; P = .038), and ABI (OR 0.002; 95% CI 0–0.68; P = .030) were independent predictor of cardiogenic SCI. We also performed the same analyses for lacunar SCI (Table 3). Univariable analysis showed that age (P = .007), hypertension (P = .037), congestive heart failure (P = .040), LAD (P = .013), LAVI (P = .017), and CAVI (P = .004) were significant risk factors (Table 3). Multivariable logistic regression analysis was not performed due to the lack of sufficient number of patients with lacunar SCI.

Discussion

The main findings of the present study were that (1) both CHA_2DS_2-VASc and $CHADS_2$ scores are useful for screening SCI in AF patients, although no patients with CHA_2DS_2-VASc score 0 had SCI on MRI; (2) SCIs localized to the cerebral cortex and cerebellum are frequently noted in AF patients, for which cardiogenic mechanisms may be mainly involved; and (3) independent risk factors for cardiogenic SCI were LA abnormality, AF duration, and ABI, whereas lacunar SCI was associated with atherosclerotic parameters but not with LA abnormality. To the best of our knowledge, this is the first study to demonstrate the characteristics and risk factors of SCI, with particular attention to its localization in AF patients.

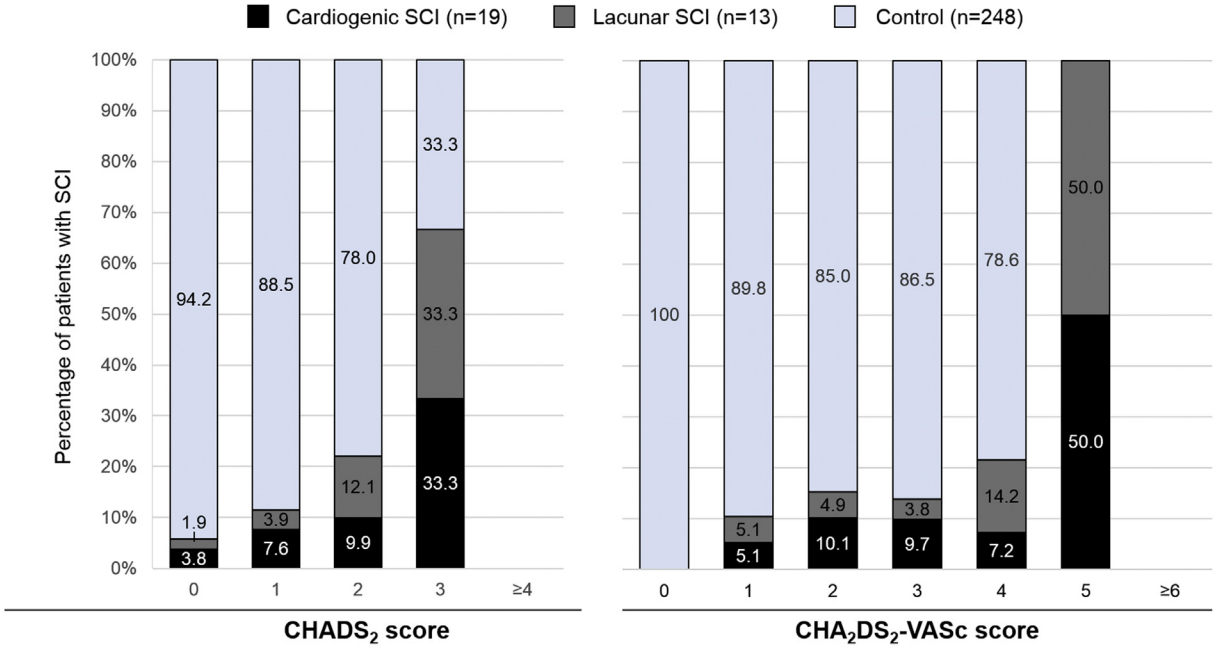
Prevalence of SCI in AF patients

In previous population-based studies, the prevalence of MRI-diagnosed SCI in the general population was between 8% and 28%,[2,7] and AF was associated with a >2-fold increase in the odds for SCI.[2,5,6] Moreover, it has been reported that the majority (>90%) of SCIs correspond to the morphology of lacunar infarcts, and that larger subcortical or cortical infarcts accounted for the remaining 10%.[7] In the present study with relatively younger AF patients, the total prevalence of SCI was 14.5%, and cardiogenic SCI accounted for one-half of the disorder. One reason for the difference in the prevalence of cardiogenic SCI between the present and the previous studies may be partly due to patient characteristics. In the present study, the patients with relatively low cardiovascular risks were apparently associated with a higher prevalence of cardiogenic and lacunar SCI. However, these results



No. of Cerebral lesions	1	2	3	4	0	0	1	1	1	2	4
No. of Cerebellar lesions	0	0	0	0	1	2	0	1	2	0	0
No. of patients (%)	6 (46.1)	4 (30.7)	1 (7.6)	2 (15.3)	4 (21.0)	1 (5.2)	9 (47.3)	1 (5.2)	1 (5.2)	1 (5.2)	2 (10.4)

Figure 2 Flowchart of classification of silent cerebral infarction (SCI) patients into 3 groups based on morphological analysis of brain magnetic resonance image: cerebral noncortical, cerebral cortical, and cerebellar lesions.



Cardiogenic SCI n (M/F)	4 (2/2)	10 (8/2)	4 (2/2)	1 (0/1)	0 (0/0)	0 (0/0)	4 (4/0)	8 (6/2)	5 (2/3)	1 (0/1)	1 (0/1)	0 (0/0)
Lacunar SCI n (M/F)	2 (2/0)	5 (4/1)	5 (5/0)	1 (1/0)	0 (0/0)	0 (0/0)	4 (4/0)	4 (4/0)	2 (1/1)	2 (2/0)	1 (1/0)	0 (0/0)
Control n (M/F)	99 (73/26)	116 (82/34)	32 (22/10)	1 (1/0)	0 (0/0)	53 (53/0)	71 (60/11)	68 (44/24)	45 (20/25)	10 (1/9)	0 (0/0)	0 (0/0)

M/F indicates the number of male / female patients.

Figure 3 $CHADS_2$ and CHA_2DS_2-VASc scores in patients with cardiogenic and lacunar silent cerebral infarction (SCI).

Table 2 Univariable and multivariable logistic regression analysis for cardiogenic SCI

	Univariable		Multivariable	
Characteristics	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.04 (0.99–1.10)	.15		
Male	0.64 (0.25–1.78)	.37		
Smoking habit	0.68 (0.23–1.82)	.46		
AF duration	1.01 (1.00–1.02)	.04	1.01 (1.00–1.02)	.04
Duration without anticoagulation	1.00 (0.99–1.01)	.14		
Nonparoxysmal AF	3.09 (1.12–8.09)	.02		
Hypertension	2.27 (0.84–7.20)	.13		
Diabetes mellitus	1.41 (0.21–5.41)	.66		
Congestive Heart failure	3.05 (0.81–9.32)	.07		
Coronary/vascular disease	3.60 (0.95–11.19)	.04	4.61 (0.80–22.13)	.06
eGFR	0.95 (0.93–0.98)	.002		
BNP	1.004 (1.001–1.007)	.004		
LVEF	0.99 (0.94–1.04)	.70		
LAD	1.04 (0.98–1.12)	.22		
LAVI	1.03 (0.99–1.06)	.15		
E/e ′	1.13 (1.01–1.26)	.02		
LAAeV	0.97 (0.95–0.99)	.03		
SEC	3.31 (1.31–8.35)	.01		
LA abnormality	5.40 (1.95–14.39)	.001	8.99 (2.78–31.00)	<.001
CAVI	1.21 (0.83–1.76)	.31		
ABI	0.010 (0–1.77)	.07	0.002 (0–0.68)	.03

CI = confidence interval; OR = odds ratio; see Table 1 for other abbreviations.

could also suggest that microembolization without apparent neurological deficits in younger AF patients is common, although these individuals were otherwise healthy persons and had relatively low $CHADS_2$ and CHA_2DS_2-VASc scores.

Usefulness of risk stratification by $CHADS_2$ vs CHA_2DS_2-VASc score

The $CHADS_2$[13] and CHA_2DS_2-VASc[14] risk scores are the most commonly used scoring systems for evaluation of stroke risk in AF patients. In the present study, we examined the predictive value of the scoring systems for occurrence of SCI. The present study demonstrates that both CHA_2DS_2-VASc and $CHADS_2$ scores are useful for screening SCI in AF patients, although no patients with CHA_2DS_2-VASc score of 0 had SCI on MRI.

Table 3 Univariable logistic regression analysis for lacunar SCI

	Univariable	
Characteristics	OR (95% CI)	*P* value
Age	1.09 (1.02–1.17)	.01
Male	1.86 (0.58–8.24)	.34
Smoking habit	1.24 (0.42–3.57)	.68
AF duration	0.99 (0.98–1.01)	.55
Duration without anticoagulation	0.99 (0.96–1.01)	.52
Nonparoxysmal AF	1.42 (0.47–3.87)	.51
Hypertension	3.85 (1.22–17.01)	.04
Diabetes mellitus	1.62 (0.24–6.30)	.54
Congestive Heart failure	3.54 (0.93–11.08)	.04
Coronary/vascular disease	1.62 (0.25–6.31)	.54
eGFR	0.98 (0.96–1.01)	.25
BNP	1.002 (0.998–1.005)	.29
LVEF	0.96 (0.92–1.01)	.07
LAD	1.11 (1.02–1.21)	.01
LAVI	1.04 (1.01–1.08)	.02
E/e ′	0.98 (0.84–1.13)	.82
LAAeV	0.98 (0.96–1.00)	.21
SEC	0.37 (0.02–1.90)	.34
LA abnormality	0.37 (0.02–1.90)	.34
CAVI	1.77 (1.20–2.66)	.004
ABI	9.61 (0.040–3737.0)	.44

See Table 1 for abbreviations.

Risk factors for cardiogenic SCI

In symptomatic cardiogenic cerebral thromboembolism, LAA has long been considered to be a primary site for thrombus formation in AF patients, and decreased peak LAA emptying velocity and SEC have been considered risk factors of cardioembolism.[10] In primate models, only <6% of emboli injected into carotid arteries entered the lenticulostriate arteries, whereas the majority entered the cortical arteries.[18] Moreover, persistence of AF elicits fibrotic changes of atrial myocardium and induces loss of atrial contraction and fibrillating motion, which would increase the risk of thrombosis in AF patients.[19] These studies suggested that cortical cerebral infarction may occur more frequently in AF patients, especially those with abnormal LA function. A similar mechanism may be involved in the pathophysiology of SCI. Sugioka et al[11] found a high prevalence of SCI in AF patients with LA abnormalities compared to those without SCI. They suggested that, in AF patients, microembolization of small thrombi from the fibrillating LA appendage may play an important role in the occurrence of SCI.[11] Although these results suggest that AF patients have a higher risk for cardiogenic SCI than general population, detailed analysis remains to be performed. In the present study, we examined morphological classification of SCI for the first time, and multiple logistic regression analyses

showed that AF duration and LA abnormality were independent predictors of cardiogenic SCI. Furthermore, low ABI was also shown to be a significant and independent predictor of cardiogenic SCI. Based on these observations, the present results indicate that SCI in cortical and cerebellar regions observed in AF patients is likely to be associated with atherosclerosis in general and cardiogenic thrombotic mechanisms in particular.

Risk factors for lacunar SCI

The present study demonstrates that CAVI, age, hypertension, and congestive heart failure are associated with lacunar SCI. CAVI, which includes measurements of pulse wave velocity and blood pressure, is an index that reflects the stiffness of the whole arterial segment, from the aorta to the tibial artery.[16] CAVI has been shown to be related to progression of cerebral small vessel diseases.[16] In addition, conventional vascular risk factors, such as age and hypertension, were also identified as risk factors for lacunar SCI.[1] LAD and LAVI were also associated with lacunar SCI. It has been observed that vascular stiffening is accompanied by changes in left ventricular stiffness and diastolic compliance.[20] LA enlargement could be one of the markers related to such ventricular abnormality. It was previously suggested that left ventricular diastolic dysfunction is one of the causes of LA enlargement, which could be related to endothelial dysfunction.[21] Taken together, arteriolar and capillary dysfunction as evidenced by CAVI and other vascular risk factors may precipitate microcirculation failure in the brain, resulting in lacunar SCI in AF patients.

Study limitations

The present study had several limitations. First, the present study was a single-center study, and our results were obtained from patients who were candidates for AF catheter ablation and had relatively low $CHADS_2$ and CHA_2DS_2-VASc scores. AF patients with extremely larger LAs would not be indicated for catheter ablation because of the higher recurrence rate of AF.[12] Thus, caution is needed when discussing the present findings in the general population. Second, the present results depend on the sensitivity and specificity of brain MR scan and the diagnostic criteria of SCI used.[17] However, because 2 radiologists independently and carefully checked brain MRI images before AF ablation and made the SCI classifications, the present results may be more accurate compared with previous studies. Third, in the present study, the exact onset time of SCI is unknown, and it is possible that SCI might have occurred before administration of anticoagulant therapy. Fourth, the type of heart rhythm (sinus/AF) at the time of echocardiography and MRI was not analyzed, which may have affected the quantitative parameters. Fifth, multivariable logistic regression analysis to identify the risk factors for lacunar SCI was not performed due to the lack of sufficient number of patients with lacunar SCI. Therefore, identified factors might be the only confounding factor for predicting lacunar SCI. Sixth, we were unable to demonstrate which type of symptomatic cerebral infarction would occur in patients with SCI. This issue remains to be examined in future longitudinal studies. Seventh, we were unable to examine whether AF patients with cardiogenic SCI could benefit from AF catheter ablation more than those without it. Although Yamamoto et al[22] showed that AF catheter ablation significantly decreases the percentage of LA abnormality, further studies are needed to elucidate whether AF catheter ablation effectively prevents cardiogenic SCI.

Conclusion

In the present study, we were able to demonstrate that among AF patients, SCIs localized in the cerebral cortex and cerebellum are frequently noted, for which cardiogenic mechanisms may be mainly involved; the CHA_2DS_2-VASc score is useful for screening SCI; and LA abnormality is the specific marker for cardiogenic SCI, providing useful information for risk stratification of SCI among these patients.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2019.03.013.

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