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Abstract

Background

Patients with atrial fibrillation (AF) often show a high prevalence of silent brain infarction (SBI), which is an independent risk factor for the development of symptomatic stroke. The left atrial emptying fraction (LAEF) is also known to be associated with an increased risk of symptomatic stroke in patients with AF; however, little is known regarding the association between SBI and LAEF in patients with paroxysmal AF.

Methods

We investigated 77 neurologically asymptomatic patients with paroxysmal AF (56 men, median age 66 years) who were scheduled to undergo transcatheter pulmonary vein isolation or electrical cardioversion. All patients underwent brain magnetic resonance imaging to screen for SBI prior to the scheduled ablation or cardioversion. Comprehensive transthoracic echocardiography was performed to calculate the LAEF.

Results

SBI was observed in 21 patients (27%). Univariate analysis showed a negative association between LAEF and SBI [odds ratio (OR) 0.92, 95% confidence interval (CI) 0.87-0.98, p=0.005]. Receiver operating characteristic curve analysis indicated that the optimal cut-off value for SBI (area under the curve 0.70) was 45.5% with a sensitivity of 62% and a specificity of 79%. Multivariate logistic regression analysis indicated that LAEF <45.5% remained independently associated with SBI (OR 6.35, 95% CI 1.82-22.1, p=0.004) after adjusting for the CHA_2DS_2-VASc score and the estimated glomerular filtration rate.

Conclusions

An impaired LAEF is associated with SBI in patients with paroxysmal AF and might be a useful parameter for risk stratification. Intensive intervention in high-risk patients may avoid SBI and reduce the subsequent stroke risk.

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Key Words: Paroxysmal atrial fibrillation; Silent brain infarction; Echocardiography; Left atrial emptying fraction

Introduction

Recent studies have focused on silent brain infarction (SBI) that is incidentally detected on brain magnetic resonance imaging (MRI) in patients with atrial fibrillation (AF)[1]. In patients presenting with SBI, most infarcts (80%-90%) are subcortical in location, and this condition is, therefore, classified as small-vessel occlusive disease or lacunar infarction caused by lipohyalinosis, microatheromas, or emboli[2]. The remaining (10%-20%) infarcts are cortical or large infarcts that are more likely to be secondary to cardiac embolism[2]. Because AF is associated with both micro- and macro-embolism[3,4], the American Heart Association/American Stroke Association statement recommends screening for AF in patients presenting with SBI[2]. Moreover, SBI is detected in approximately 25% of patients with AF who report no history of stroke[5] and is associated with occurrence of a stroke in future[6] or cognitive decline[7] in patients with AF. Therefore, identification of high-risk patients who may benefit from more intensive interventions is important to provide customized treatment for each patient, which is aimed at prevention of SBI.

Assessment of left atrial (LA) function could be an alternative strategy to facilitate risk stratification beyond traditional risk factors among AF patients with SBI. Impaired LA function is associated with an increased risk of an LA thrombus or thromboembolism[8-12]. However, the association between LA function (i.e., LA emptying function; LAEF) and the presence of SBI has not been addressed by clinical studies.

We aimed to assess the relationship between LAEF and the presence of SBI in patients with paroxysmal AF.

Methods

This cross-sectional single center study included 213 consecutive, neurologically asymptomatic patients with nonvalvular AF who underwent percutaneous pulmonary vein isolation or electrical cardioversion between 2011 and 2015 at the Osaka City University Hospital. We excluded patients who had undergone prior pulmonary vein isolation or any valve replacement procedure, those diagnosed with mitral stenosis, and those without MRI findings because of contraindications or patient's refusal. We selected 77 patients diagnosed with paroxysmal AF from among the remaining 157 patients. Paroxysmal AF was diagnosed in patients with a history of AF in whom an electrocardiogram indicated sinus rhythm when transthoracic echocardiography (TTE) was performed. The study protocol conformed to the guidelines of the Declaration of Helsinki (Second Revision, 1983) and was approved by the Ethics Committee of the hospital (approval number: 3214). Written informed consent was obtained from each patient prior to inclusion in the study.

Clinical variables such as age, body mass index, hypertension, diabetes mellitus, dyslipidemia, congestive heart failure, vascular disease, smoking status, chronic kidney disease, and information regarding prior treatment were obtained for each patient. Hypertension was defined as patient-reported history of hypertension, a systolic blood pressure ≧140 mm Hg or a diastolic blood pressure ≧90 mm Hg upon admission, or treatment with an oral antihypertensive drug[13]. Diabetes mellitus was defined as a fasting blood glucose level ≧126 mg/dL, a hemoglobin A1c (HbA1c) level ≧6.5%, existing diagnosis of diabetes mellitus or the reported use of an oral hypoglycemic drug[14].

Dyslipidemia was defined as a serum cholesterol level ≧220 mg/dL or a low-density lipoprotein cholesterol level ≧140 mg/dL upon admission or the reported use of a cholesterol-lowering drug[15]. A history of vascular disease was defined as the presence of myocardial infarction or peripheral artery disease. Patients were classified as non-smokers if they had never smoked or if they had stopped smoking for ≧10 years prior to inclusion in this study. Chronic kidney disease was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2 (category ≧G3)[16,17]. We calculated the CHA_2DS_2-VASc score using the above information[18]. Duration of paroxysmal AF and anticoagulation therapy was determined from the patients' reports or medical records and were categorized into 2 groups: duration <6 months or ≧6 months.

All enrolled patients underwent 2-dimensional TTE that was performed using commercially available systems with patients placed in the left lateral decubitus position. Echocardiographic quantification was performed based on the American Society of Echocardiography guidelines[19]. End-diastolic left ventricular (LV) diameter, end-systolic LV diameter, end-diastolic interventricular septal thickness, end-diastolic LV posterior wall thickness, and LV ejection fraction were measured. The LV mass was calculated based on the LV linear dimensions using the following formula: {0.8×1.04×[(end-diastolic LV diameter+end-diastolic LV posterior wall thickness+end-diastolic interventricular septal thickness)^3−(end-diastolic LV diameter)^3]+0.6} g and was indexed to the body surface area. Maximal and minimal LA volumes were measured using the biplane modified Simpson's method using apical 4- and 2-chamber views. The maximal LA volume was obtained just prior to the opening of the mitral valve, and the minimal LA volume was obtained at the moment of mitral valve closure. Indexed LA volumes (LAVI) were calculated based on the patient's body surface area. These data were used to calculate the LAEF using the formula: LAEF=[(maximal LAVI−minimal LAVI)/maximal LAVI]×100[20] (Fig. 1). Early E and late A transmitral velocities were measured using a pulsed-wave Doppler based on the apical 3-chamber view with the sample volume positioned at the tip of the mitral leaflets[21].

All MRI examinations were performed using a 3.0-Tesla (T) unit (Achieva Quasar Dual; Philips Medical Systems, Best, The Netherlands) or a 1.5-T unit (Achieva Nova Dual; Philips Medical Systems, Best, The Netherlands) with a standard head coil. Axial T1-weighted images (3.0-T unit: repetition time 400 ms, echo time 15 ms, field of view 220 mm^2, imaging matrix 256×181, 5 mm thickness and 1 mm gap; 1.5-T unit: repetition time 737 ms, echo time 15 ms, field of view 220 mm^2, imaging matrix 256×180, 5 mm thickness and 1 mm gap) and axial T2-weighted images (3.0-T unit: repetition time 4000 ms, echo time 90 ms, field of view 220 mm^2, imaging matrix 448×300, 5 mm thickness and 1 mm gap; 1.5-T unit: repetition time 4560 ms, echo time 90 ms, field of view 220 mm^2, imaging matrix 352×272, 5 mm thickness and 1 mm gap) were obtained to evaluate SBI. SBI was defined as an area of low intensity observed on T1-weighted images and an area of high intensity observed on T2-weighted images with a diameter ≧3 mm[22] (Fig. 2). Lesions that demonstrated a high intensity on diffusion images were excluded from the analysis. The presence of SBI was confirmed by an experienced neuroradiologist (S.S.) who had been blinded to the clinical information of the patients enrolled in this study.

Statistical methods

Continuous variables were expressed as median values (interquartile ranges), and categorical variables as numbers and percentages. The distribution of clinical or echocardiographic variables was evaluated among patients with SBI versus those without SBI. We compared the groups using

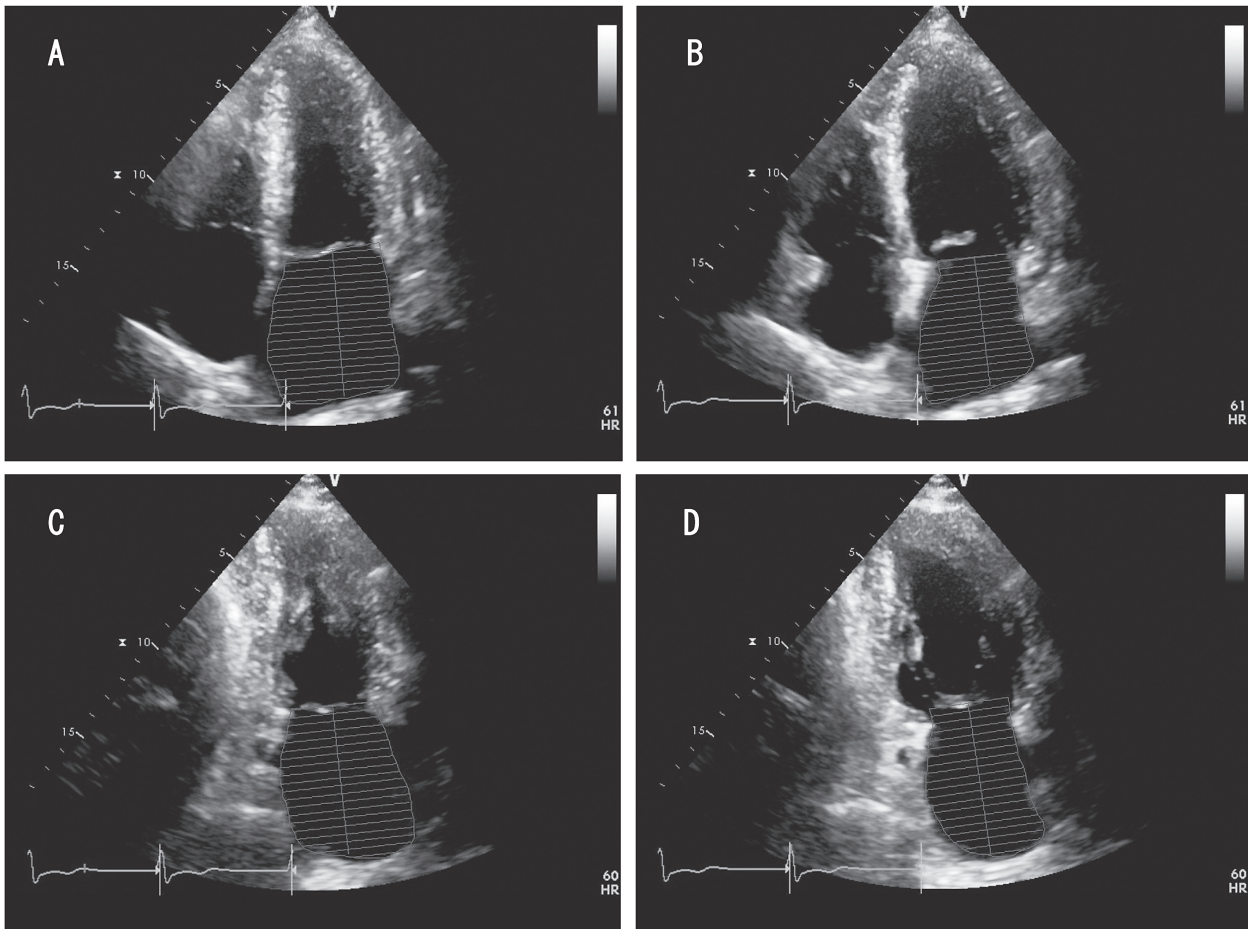

Figure 1. Echocardiographic assessment of left atrial volume using the biplane modified Simpson's method.
A=maximal left atrial volume using apical 4-chamber view.
B=minimal left atrial volume using apical 4-chamber view.
C=maximal left atrial volume using apical 2-chamber view.
D=minimal left atrial volume using apical 2-chamber view.

the unpaired *t* test for continuous variables with a normal distribution and the Mann-Whitney U test for continuous variables with a non-normal distribution. Categorical variables were compared using a chi-square test or the Fisher exact test (N ≧20). Univariate logistic regression analysis was performed to identify clinical and echocardiographic variables that were associated with the presence of SBI. A p value of <0.05 (except with regard to age and diabetes mellitus, which were included in the CHA_2DS_2-VASc score) was used to select variables that would be subjected to multiple logistic regression analysis. Moreover, we performed multivariate logistic regression analysis using propensity score as a covariate to minimize the potential selection bias. Because the cut-off value is useful for risk stratification in clinical settings, we used LAEF as a binary variable (LAEF <45.5% or ≧45.5%), which is the optimal cut-off value for predicting the presence of SBI (area under the curve 0.70) with a sensitivity of 62% and a specificity of 79% derived from receiver operating characteristic curve analysis. The covariates in Model 1 included the LAEF and the propensity score derived from the general risk factors for SBI (age, HbA1c, low-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, smoking, and estimated glomerular filtration rate) which had a concordance index of 0.70. The covariates in Model 2 included the LAEF and the propensity score derived from

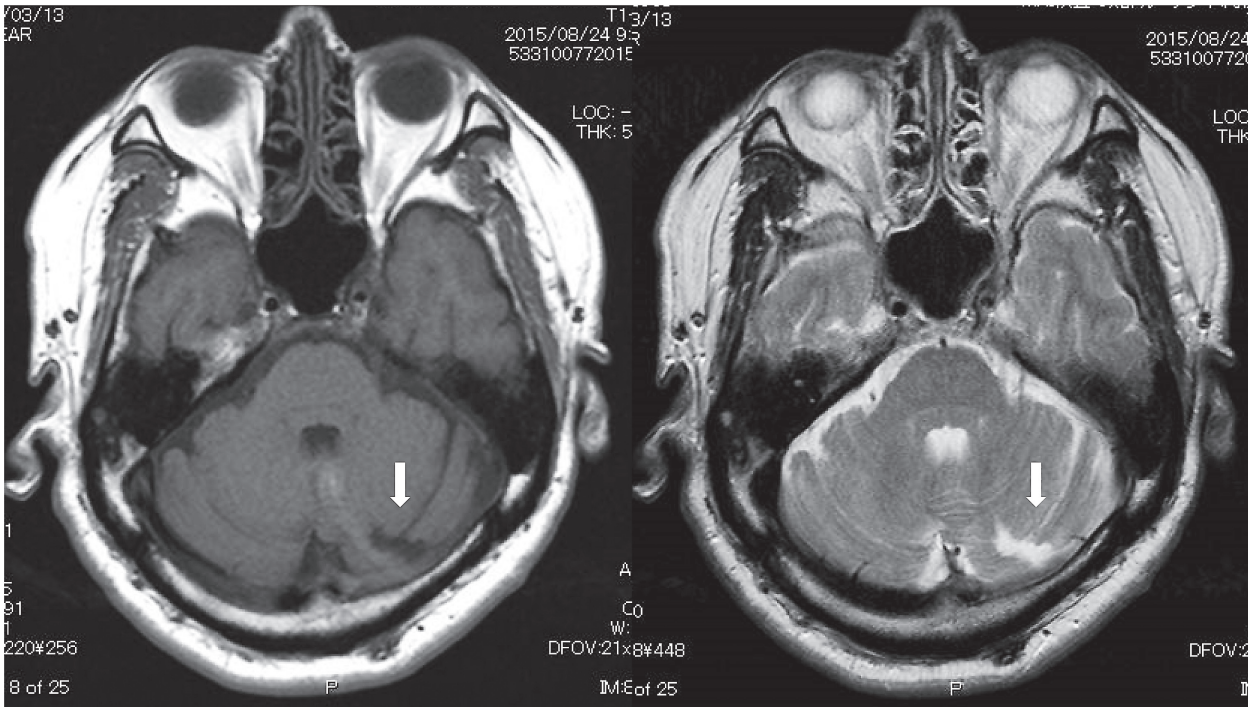

Figure 2. A representative case of silent brain infarction (SBI). This patient shows SBI in the left cerebellar hemisphere (arrow) concomitant with paroxysmal atrial fibrillation and a decreased left atrial emptying fraction (43%).

the variables associated with the presence of SBI noted using univariate analysis (age, congestive heart failure, hemoglobin, estimated glomerular filtration rate, antiplatelet drug usage, and angiotensin-converting enzyme inhibitor/angiotensin Ⅱ receptor blocker usage) which had a concordance index of 0.72. We also used inverse probability of treatment weighting method in these 2 models to confirm our results. We used dummy variables for analyses as following; 1=male, 0=female; 1=smoker, 0=non-smoker; 1=duration of atrial fibrillation ≧6 months, 0=duration of atrial fibrillation <6 months; 1=duration of anticoagulant usage <6 months, 0=duration of anticoagulant usage ≧6 months; 1=LAEF <45.5%, 0=LAEF ≧45.5%; other clinical variables and usage of medications: 1=presence, 0=absence. p values <0.05 were considered statistically significant. All statistical analyses were carried out using SPSS version 24 (IBM Corp., Armonk, NY, USA).

Results

Among the 77 patients diagnosed with paroxysmal AF, SBI was observed in 21 (27%). Among these 21 patients, subcortical and small (3-15 mm) infarcts were detected in 15, cortical or large infarcts in 14, and both varieties in 8. Baseline clinical characteristics of patients with and without SBI are shown in Table 1. All patients had been administered anticoagulants. Age, diabetes mellitus, congestive heart failure, chronic kidney disease, the CHA_2DS_2-VASc score, and use of antiplatelet agents and angiotensin-converting enzyme inhibitor/angiotensin Ⅱ receptor blockers were variables that were observed to be positively associated with the presence of SBI. Hemoglobin and estimated glomerular filtration rate were variables that were negatively associated with the presence of SBI. Echocardiographic characteristics of patients with and without SBI are shown in Table 2. LAEF was negatively associated with the presence of SBI, whereas the other variables including the LV ejection fraction, LV mass index, maximal LAVI, and mitral E velocity were not associated with the presence

Table 1. Baseline clinical characteristics of patients with and without silent brain infarction

	SBI (+) (N=21)	SBI (−) (N=56)	p
Age, years	68 (66-74)	65 (54-70)	0.01
Males, n (%)	16 (76)	40 (71)	0.68
Body mass index, kg/m^2	25 (23-27)	24 (22-27)	0.18
Hypertension, n (%)	16 (76)	31 (55)	0.10
Systolic blood pressure, mm Hg	126 (120-136)	130 (113-135)	0.97
Diastolic blood pressure, mm Hg	71 (69-78)	76 (69-80)	0.24
Diabetes mellitus, n (%)	8 (38)	9 (16)	0.04
Smoker, n (%)	7 (33)	20 (36)	0.85
Dyslipidemia, n (%)	6 (29)	22 (39)	0.38
Congestive heart failure, n (%)	6 (29)	1 (2)	0.001
Duration of atrial fibrillation (≧6 months), n (%)	11 (52)	41 (73)	0.08
Duration of anticoagulant usage (<6 months), n (%)	8 (30)	28 (50)	0.35
Hemoglobin A1c, %	5.8 (5.7-6.2)	5.7 (5.5-6.0)	0.05
Total cholesterol, mg/dL	167 (157-197)	176 (159-188)	0.90
High-density lipoprotein cholesterol, mg/dL	41 (37-46)	43 (39-53)	0.14
Low-density lipoprotein cholesterol, mg/dL	101 (85-122)	102 (89-118)	0.98
Triglycerides, mg/dL	135 (106-176)	117 (85-153)	0.23
Albumin, g/dL	4.2 (4.2-4.3)	4.3 (4.1-4.5)	0.22
Hemoglobin, g/dL	13.6 (12.9-14.9)	14.5 (13.7-15.1)	0.04
C-reactive protein, mg/dL	0.09 (0.05-0.11)	0.08 (0.02-0.14)	0.31
eGFR, mL/min/1.73m^2	60 (48-73)	70 (62-82)	0.004
Chronic kidney disease, n (%)	10 (48)	12 (21)	0.02
CHA_2DS_2-VASc score	3.0 (2.0-4.0)	1.5 (1.0-2.3)	0.003
Medications			
Antiplatelet agents, n (%)	3 (14)	0 (0)	0.02
Anticoagulants, n (%)	21 (100)	56 (100)	-
Vitamin K antagonists, n (%)	7 (33)	11 (20)	0.17
Direct oral anticoagulants, n (%)	14 (67)	45 (80)	0.17
Antiarrhythmic agents, n (%)	13 (62)	34 (61)	0.92
Statins, n (%)	6 (29)	15 (27)	0.88
ACEI/ARB, n (%)	29 (38)	12 (16)	0.001
Calcium channel blockers, n (%)	8 (38)	15 (27)	0.33
β-blocker, n (%)	9 (43)	15 (27)	0.18
Antidiabetic medication, n (%)	6 (29)	6 (11)	0.06

Continuous variables were expressed as median values (interquartile ranges), and categorical variables as numbers and percentages. SBI, silent brain infarction; eGFR, estimated glomerular filtration rate; ACEI, angiotensin-converting enzyme inhibitor; and ARB, angiotensin Ⅱ receptor blocker.

of SBI. Table 3 shows the clinical and echocardiographic variables associated with the presence of SBI and their OR obtained using univariate and multivariate analysis. LAEF (as a continuous variable) was inversely associated with the presence of SBI after adjusting for the CHA_2DS_2-VASc score and the estimated glomerular filtration rate (OR 0.92, 95% CI 0.86-0.98, p=0.007). Moreover, the CHA_2DS_2-VASc score (OR 1.94, 95% CI 1.11-3.40, p=0.02) and the LAEF <45.5% (OR 6.35, 95% CI 1.82-22.13, p=0.004), which is the optimal cut-off value for predicting the presence of SBI (area under the curve 0.70) with a sensitivity of 62% and a specificity of 79% derived from receiver operating characteristic curve analysis, remained independently associated with the presence of SBI after adjusting for the estimated glomerular filtration rate. Furthermore, LAEF <45.5% (a binary

Table 2. Echocardiographic findings in patients with and without silent brain infarction

	SBI (+) (N=21)	SBI (−) (N=56)	p
End-diastolic left ventricular diameter, mm	49 (43-55)	47 (44-49)	0.37
End-systolic left ventricular diameter, mm	30 (26-35)	28 (26-31)	0.21
Interventricular septal thickness, mm	9 (9-10)	9 (8-10)	0.09
Posterior wall thickness, mm	9 (8-10)	9 (8-10)	0.45
Left atrial diameter, mm	41 (38-46)	39 (34-43)	0.07
Left ventricular ejection fraction, %	60 (55-60)	60 (60-60)	0.08
Mitral E velocity, cm/s	65 (48-77)	60 (55-66)	0.63
Mitral A velocity, cm/s	63 (44-75)	63 (48-80)	0.87
Mitral E deceleration time, ms	246 (229-275)	225 (190-255)	0.63
Left ventricular mass index, g/m^2	103 (93-125)	98 (89-115)	0.10
Maximal left atrial volume index, mL/m^2	36 (29-45)	35 (27-41)	0.15
Left atrial emptying fraction, %	43 (36-56)	53 (47-60)	0.002

Continuous variables were expressed as median values (interquartile ranges), and categorical variables as numbers and percentages. SBI, silent brain infarct.

Table 3. Clinical and echocardiographic variables associated with silent brain infarction

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age, per 1year	1.08 (1.01-1.15)	0.08		
Male sex	1.28 (0.40-4.08)	0.68		
Diabetes mellitus	3.21 (1.04-9.98)	0.04		
Hypertension	2.58 (0.83-8.02)	0.10		
Dyslipidemia	0.62 (0.21-1.83)	0.38		
Smoking	0.90 (0.31-2.60)	0.85		
Estimated glomerular filtration rate, per 1 mL/min/1.73m^2	0.95 (0.92-0.99)	0.01	0.98 (0.94-1.02)	0.23
Chronic kidney disease	3.33 (1.15-9.70)	0.03		
Duration of anticoagulant use <6 months	0.62 (0.22-1.72)	0.35		
Duration of atrial fibrillation ≧6 months	0.40 (0.14-1.14)	0.09		
CHA_2DS_2-VASc score, per 1point	2.02 (1.27-3.20)	0.003	1.94 (1.11-3.40)	0.02
Left ventricular mass index, per 1 g/m^2	1.02 (1.00-1.05)	0.10		
Maximal left atrial volume index, per 1 mL/m^2	1.03 (0.99-1.06)	0.15		
Left atrial emptying fraction, per 1%	0.92 (0.87-0.98)	0.005		
Left atrial emptying fraction <45.5%	5.96 (2.01-17.68)	0.001	6.35 (1.82-22.13)	0.004

OR, odds ratio; and CI, confidence interval.

variable) remained independently associated with the presence of SBI using propensity scores (Table 4). Finally, we confirmed the significant association between LAEF <45.5% and the presence of SBI using inverse probability of treatment weighting method (model 1; OR 5.26, 95% CI 1.64-16.91, p=0.005, model 2; OR 3.75, 95% CI 1.15-12.21, p=0.03).

Discussion

In the present study, we observed that an impaired LAEF was significantly associated with the presence of SBI in patients with paroxysmal AF after adjusting for accepted risk factors or the CHA_2DS_2-VASc score and the estimated glomerular filtration rate. These results suggest that an

Table 4. Multivariate logistic regression analysis for silent brain infarction: Propensity score adjustment

	Model 1		Model 2	
	OR (95% CI)	p	OR (95% CI)	p
LAEF <45.5%	6.08 (1.89-19.60)	0.003	3.88 (1.20-12.61)	0.024

Model 1 adjusts for the propensity score derived from the general risk factors of silent brain infarction (age, hemoglobin A1c, low-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, smoking, and estimated glomerular filtration rate). Model 2 adjusts for the propensity score derived from variables associated with silent brain infarction noted using univariate analysis (age, congestive heart failure, hemoglobin, estimated glomerular filtration rate, antiplatelet drug usage, and angiotensin-converting enzyme inhibitor/angiotensin Ⅱ receptor blocker usage). OR, odds ratio; CI, confidence interval; and LAEF, left atrial emptying fraction.

impaired LAEF may be associated with microthrombus formation, which is a risk factor for the presence of SBI in patients with paroxysmal AF. To our knowledge, this is the first study to demonstrate that LAEF (calculated using TTE) is associated with the presence of SBI in patients with paroxysmal AF.

Our study showed that LAEF was statistically significantly associated with the presence of SBI — a finding that is in agreement with that of previous studies showing that the LA function plays an important role in predicting SBI. The Cardiovascular Abnormalities and Brain Lesions (CABL) study showed that LAEF assessed using echocardiography was significantly associated with the presence of SBI in the general population without a history of stroke[23]. However, this study primarily focused on patients with a sinus rhythm. To date, no study has investigated the influence of LAEF on the presence of SBI in patients with paroxysmal AF.

Our study revealed that LAEF is associated with the presence of SBI in patients with paroxysmal AF. Based on our results, we hypothesized that an impaired LAEF plays an important role in the progression of thrombogenesis in the LA with the subsequent development of SBI in patients with paroxysmal AF. The mechanisms underlying our finding remain unclear. There is, however, considerable evidence to explain the role of impaired LAEF in the process of thrombogenesis. Impaired LAEF has been proven to be associated with the presence of an LA thrombus, which leads to the development of a symptomatic stroke in patients with AF[11]. Similarly, an impaired LAEF is known to be associated with spontaneous echo contrast, which is a risk factor for cerebral microembolism in patients with AF[11]. Moreover, LAEF is associated with the CHA_2DS_2-VASc score[12], which is a well-accepted tool for risk stratification with regard to thrombogenesis or symptomatic stroke in patients with AF. Although we focused only on paroxysmal AF, LAEF itself may accelerate LA thrombogenesis and cause subsequent SBI even in patients with paroxysmal AF.

A few studies have reported that LAVI was shown to be associated with the presence of SBI in patients with AF[8-10]; however, our study showed no association between LAVI and SBI in patients with paroxysmal AF. This difference might be at least partly attributable to the differences in study cohorts (studies that investigated any type of AF vs our study that investigated only paroxysmal AF). Impaired LAEF is known to be an earlier stage of abnormality than that noted in LA enlargement[24]. Paroxysmal AF may indicate a shorter history of AF; thus, LAEF may be a better predictor than LAVI to predict the presence of SBI in patients with paroxysmal AF.

Limitations

Limitations of our study: 1) Our study included a relatively small number of patients. Thus, future

studies including a larger number of patients are necessary to confirm whether LAEF is significantly associated with the presence of SBI. 2) Because cross-sectional data cannot investigate causality, a prospective study would be necessary to establish whether LAEF can conclusively predict the presence of SBI. 3) Because our study population comprised patients scheduled for transcatheter pulmonary vein isolation or electrical cardioversion, a selection bias might have influenced our study results. 4) Because it is difficult to ascertain the mechanisms of SBI (particularly in patients presenting with lacunar infarction), there exists the possibility that our study also included non-embolic causes of SBI. 5) Although a 1.5-T MRI is an acceptable modality for the assessment of SBI, the detection rate of SBI may be different between 1.5-T and 3.0-T MRI testing[25]. 6) This study did not evaluate the LA parameters using novel methods such as a 3-dimensional echocardiographic method[26] or the speckle tracking method[27].

Conclusions

Impaired LAEF is associated with the presence of SBI in patients with paroxysmal AF, and LAEF might be a useful parameter for risk stratification of thromboembolism in patients presenting with paroxysmal AF.

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