Predictors of Left Atrial Thrombi and Spontaneous Echocardiographic Contrast in the Acute Phase After Cardioembolic Stroke in Patients With Atrial Fibrillation

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Introduction: The underlying mechanism of the residual left atrial thrombus (LAT)/spontaneous echo contrast (SEC) after the onset of cardioembolic stroke (CES) is unknown. This study aims to investigate the utility of $CHADS_2$ and CHA_2DS_2-VASc scores for predicting LAT/SEC, and to investigate the risk factors of residual LAT/SEC after CES onset. *Methods:* This retrospective study included 124 patients who were admitted with the acute phase of CES at our center. The clinical, echocardiographic variables, the $CHADS_2$/CHA_2DS_2-VASc scores, and National Institutes of Health Stroke Scale score were retrospectively assessed on admission. *Results:* Of 124 patients, LAT or SEC was detected in 39 patients (31.5%, 17 LAT and 38 SEC). Univariate analysis showed that the LAT/SEC group had a higher prevalence of nonparoxysmal atrial fibrillation (AF), left ventricular (LV) hypertrophy, hypertension, the rate of anticoagulation before admission, higher National Institutes of Health Stroke Scale score, larger left atrial diameter, and elevated E wave. In contrast, the $CHADS_2$ and CHA_2DS_2-VASc scores were not associated with LAT/SEC. LAT/SEC was associated with nonparoxysmal AF and LV hypertrophy on multivariate analysis. Moreover, all patients were divided into 4 groups based on the combination between non-paroxysmal AF and LV hypertrophy. The rate of LAT/SEC was the highest (87.5%) in patients with nonparoxysmal AF and LV hypertrophy. *Conclusions:* Nonparoxysmal atrial fibrillation and left ventricular hypertrophy were associated with residual left atrial thrombus/spontaneous echo contrast in the acute phase after cardioembolic stroke that was independent of the $CHADS_2$ and CHA_2DS_2-VASc scores.

Key Words: Stroke—Thrombus—Left ventricular hypertrophy—Atrial fibrillation

Introduction

Atrial fibrillation (AF), a common arrhythmia type, predisposes the patient to left stasis and subsequent left atrial thrombus formation, which can lead to cardioembolic stroke (CES). In the Framingham study, AF increased stroke risk by 5-fold and was associated with increased mortality.[1,2] Although endovascular therapies have been making progress,[3-5] AF-associated strokes are still devastating, and AF is a predictive factor for severe stroke and early death. In particular, re-embolization after the onset of CES is often devastating, and is associated with the outcome. Little has been reported on re-embolization, and the predominant view is that the residual LAT/spontaneous echo contrast (SEC) might cause the re-embolization.

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However, the underlying mechanism of the residual LAT/SEC is unknown. This study aims to investigate the utility of $CHADS_2$ and CHA_2DS_2-VASc scores for predicting LAT/SEC, and to investigate the risk factors of residual LAT/SEC after CES onset.

Methods

Patients Population

This study included 130 patients who were admitted with the acute phase of CES at the Hyogo College of Medicine between October 2013 and April 2016. All patients underwent magnetic resonance angiography or cerebral angiography within 24 hours from the time of neurological symptoms onset, and CES was diagnosed at the end of a complete etiologic work-up by stroke neurologists; transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), carotid duplex sonography, electrocardiogram monitoring, and brain computed tomographic angiography and/or magnetic resonance angiography. From this initial population, 4 patients with poor-quality echocardiographic images, 1 patient who underwent cardiac surgery, and 1 patient with significant valvular disease were excluded. The remaining 124 patients were included in retrospective study analyses. The clinical and echocardiographic variables were retrospectively assessed. The $CHADS_2$ and CHA_2DS_2-VASc scores and National Institutes of Health Stroke Scale (NIHSS) score were calculated on admission.[6-8] All patients were divided into 2 groups using $CHADS_2$ score or CHA_2DS_2-VASc score (low risk of stroke group; $CHADS_2$ score was 0 or 1, moderate to high risk of stroke group; $CHADS_2$ score was >1) (low risk of stroke group; $CHADS_2$-VASc score was 0 or 1, moderate to high risk of stroke group; $CHADS_2$-VASc score was >1). All patients were older than 20 years, and the research protocol was approved by the appointed local ethics committee.

Echocardiographic Imaging

TTE was performed with commercially available equipment within 7 days after hospitalization. Complete 2-dimensional, M-mode, and Doppler studies were done in the left lateral decubitus position or the supine position, using the standard parasternal, apical, and subcostal views. The left atrial (LA) diameter, E wave, E/e' ratio, left ventricular (LV) diameter during end diastole, LV ejection fraction, and LV hypertrophy were assessed. Measurement of the LA diameter was obtained from parasternal long axis and apical 4-chamber views according to standard criteria. LV hypertrophy was defined as a posterior wall or interventricular septal thickness greater than 12 mm. If this thickness was less than 12 mm, the LV mass index was calculated. If the LV mass index was 95 (female) or 115 (male), the patient was considered to have LV hypertrophy. This definition of LV hypertrophy was based on the American Society of Echocardiography guideline.[9]

TEE was performed to detect residual LAT/SEC in all patients within 14 days after hospitalization. After local pharyngeal anesthesia with lidocaine spray, the patient was placed in the left lateral position, and a transesophageal transducer was inserted in the esophagus. We evaluated the presence of LAT/SEC. An LAT was defined as being present if there was a mass that could be distinguished from the surrounding endocardium or pectinate muscles.[10] SEC was defined as a pattern of dynamic "smokelike," slowly swirling, intracavitary echodensities imaged with gain settings adjusted to eliminate background noise.[10] No complications from any of the TEE procedures were reported.

Statistical Analysis

All continuous variables are expressed as the mean value ± standard deviation. Statistical comparisons were made by Student's t test. Differences between categorical variables were evaluated with a χ^2 analysis. A P value less than .05 was considered statistically significant. Univariate analyses were performed using a Student's t test or χ^2 analysis. The variables that were found to be significant in univariate analysis were entered into a multivariate analysis. The independent association with LAT/SEC was evaluated using multivariate analysis. To calculate sensitivity, specificity, positive predictive values (PPV), and negative predictive value (NPV), the receiver operating characteristics (ROC) curve was used. All analyses were performed with JMP version 12.0 software (SAS Institute, Cary, NC).

Results

All 124 patients (44 nonparoxysmal AF; 59 paroxysmal AF; 21 patients had no AF history; age 69 ± 15 years, 76 males) were enrolled in the study according to the aforementioned inclusion and exclusion criteria. Of 124 patients, LAT or SEC was detected in 39 patients (31.5%, 17 LAT and 38 SEC). All 17 patients with LAT had SEC. In 17 patients with LAT, the thrombi were located within the LA appendage. We divided all patients into 2 groups as follows: with LAT/SEC group (n = 39) and without LAT/SEC group (n = 85). The baseline characteristics of the patients are listed in Table 1. There were 44 patients (35%) with nonparoxysmal AF. Those with LAT/SEC had higher prevalence of nonparoxysmal AF and hypertension compared those without LAT/SEC. Seventeen patients (14%) had structural heart disease, which included 12 patients with nonischemic cardiomyopathy (1 hypertrophic cardiomyopathy, 8 dilated cardiomyopathies, 5 others) and 10 patients with ischemic cardiomyopathy. Structural heart disease was not significantly associated with the presence of LAT/SEC. Those in with LAT/SEC had a higher NIHSS score on admission than those without LAT/SEC.

Table 1. *Baseline characteristics and echocardiographic findings*

	With LAT/SEC (n = 39)	Without LAT/SEC (n = 85)	*P* value
Baseline characteristics			
Male, n (%)	23 (59%)	53 (62%)	.8182
Age (years)	70 ± 2	69 ± 2	.8428
Body mass index (kg/m^2)	23.4 ± .6	22.7 ± .4	.3679
Non-paroxysmal AF, n (%)	30 (77%)	14 (16%)	<.0001
Hypertension, n (%)	31 (79%)	48 (56%)	.0159
Dyslipidemia, n (%)	11 (28%)	29 (34%)	.543
Diabetes mellitus, n (%)	8 (21%)	18 (21%)	.9328
Prior congestive heart failure, n (%)	8 (21%)	8 (9%)	.1462
Prior stroke/TIA, n (%)	10 (26%)	27 (32%)	.533
Vascular disease, n (%)	28 (72%)	62 (73%)	.8943
Structural heart disease, n (%)	6 (15%)	11 (13%)	.7806
Non-ischemic cardiomyopathy, n (%)	5 (13%)	7 (8%)	.5151
Ischemic cardiomyopathy, n (%)	1 (3%)	9 (11%)	.1688
Other, n (%)	3 (8%)	2 (2%)	.1785
$CHADS_2$ score >1, n (%)	26 (67%)	51 (60%)	.4774
CHA_2DS_2-VASc score >1, n (%)	38 (97%)	78 (92%)	.4333
NIHSS score on admission	11.6 ± 8.1	6.0 ± 8.0	.0005
Serum creatinine (mg/dL)	.9 ± .5	1.1 ± 1.1	.3658
Uric acid (mg/dL)	6.1 ± 2.3	5.4 ± 1.9	.132
Anti-platelet therapy before admission, n (%)	6 (15%)	18 (21%)	.4757
Anticoagulation before admission, n (%)	15 (38%)	9 (11%)	.0005
Anticoagulation from admission to TEE, n (%)	30 (77%)	54 (64%)	.1385
Time from admission to TEE (days)	7.1 ± 3.5	6.1 ± 3.5	.1304
Echocardiographic findings			
LA diameter (mm)	47.7 ± 7.8	38.7 ± 7.1	<.0001
E wave (cm/sec)	91.1 ± 30.0	72.6 ± 21.6	.0002
E/e' ration	15.6 ± 13.5	12.5 ± 5.1	.069
LV diameter during end-diastole (mm)	46.8 ± 6.7	48.0 ± 5.5	.2809
LV ejection fraction (%)	60.5 ± 14.7	63.1 ± 12.9	.3204
LV hypertrophy, n (%)	20 (51%)	12 (14%)	<.0001

Values are given as no. (%) or mean ± SD.

Abbreviations: AF, atrial fibrillation; LA, left atrial; LAT, left atrial thrombus; LV, left ventricular; NIHSS, National Institutes of Health Stroke Scale; SEC, spontaneous echo contrast; TEE, transesophageal echocardiography; TIA, transient ischemic attack.

The proportion of patients with LAT/SEC according to the $CHADS_2$/CHA_2DS_2-VASc scores is shown in Figures 1 and 2. The prevalence of LAT/SEC was 23.1%, 29.4%, 31.6%, 38.5%, 20%, 66.7%, and 0% in patients with $CHADS_2$ scores of 0, 1, 2, 3, 4, 5, and 6, respectively (Fig 1). The prevalence of LAT/SEC was 0%, 20%, 33.3%, 29.0%, 34.8%, 44%, 21.4%, 0%, 50%, and 0% in patients with CHA_2DS_2-VASc scores of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9,

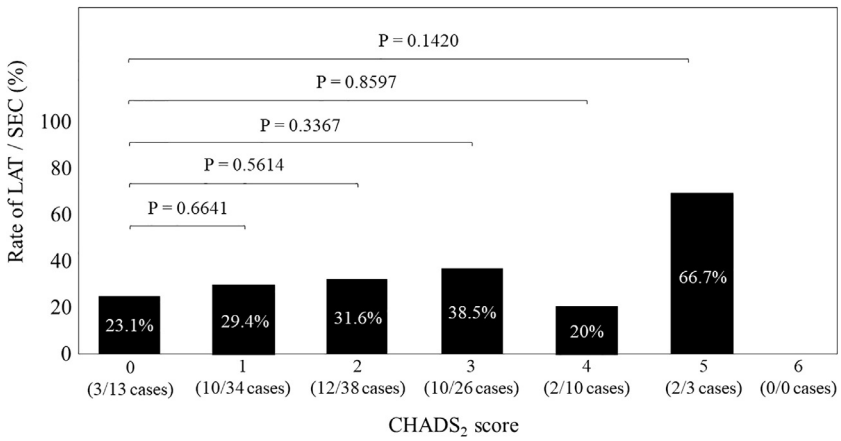

Figure 1. *Association between the $CHADS_2$ score and LAT/SEC. Abbreviations: LAT, left atrial thrombus; SEC, spontaneous echo contrast.*

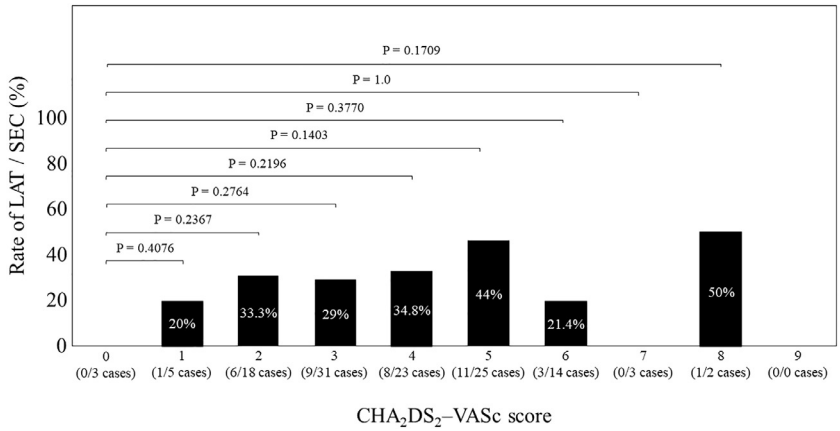

Figure 2. *Association between the CHA_2DS_2-VASc score and LAT/SEC. Abbreviations: LAT, left atrial thrombus; SEC, spontaneous echo contrast.*

Table 2. *Univariate and multivariate analyses*

	Univariate analysis	Multivariate analysis	
	P value	*P* value	OR (95%CI)
Nonparoxysmal AF	<.0001	.0006	9.039 (2.548-36.493)
LV hypertrophy	<.0001	.0207	4.342 (1.249-16.797)
Hypertension	.0159	.1889	
Oral anticoagulants before admission	.0005	.4061	
NIHSS score on admission	.0005	.1434	
LA diameter	<.0001	.1682	
E wave	.0002	.7335	

Abbreviations: AF, atrial fibrillation; CI, confidence interval; LA, left atrial; LV, left ventricular; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

respectively (Fig 2). Patients with high these scores tended to have a higher prevalence of LAT/SEC than patients with low these scores, however, there were no significant differences (Figs. 1 and 2).

The medication therapy before/after admission and echocardiographic findings are listed in Table 1. Twenty-four patients (19%) had anticoagulation therapy before admission, which include 7 patients with direct oral anticoagulants and 17 patients with warfarin. The rate of oral anticoagulants before admission was significantly higher in those with LAT/SEC than those without LAT/SEC. The use of antiplatelet therapy did not differ between those with LAT/SEC and those without LAT/SEC. Patients with LAT/SEC had significantly larger left atrial diameter, elevated E wave, and higher prevalence of LV hypertrophy than those without LAT/SEC. Eighty-four patients (68%) had anticoagulation therapy from admission to TEE (warfarin/heparin: 35 patients, direct oral anticoagulants: 49 patients). The use of anticoagulation therapy from admission to TEE did not differ between patients with LAT/SEC and those without LAT/SEC. The time from admission to TEE was also between the 2 groups.

On multivariate analysis, nonparoxysmal AF ($P = .0006$, OR 9.039, 95% CI 2.548-36.493) and LV hypertrophy ($P = .0207$, OR 4.342, 95% CI 1.249-16.797) were independently associated with the presence of LAT/SEC (Table 2). We then performed ROC curve analysis. The area under the ROC curve (AUC) of nonparoxysmal AF was .8023 ($P < .0001$, sensitivity: .7692, specificity: .8353, PPV: .6818, and NPV: .8875). The AUC of the presence of LV hypertrophy was also .6858 ($P < .0001$, sensitivity: .5128, specificity: .8588, PPV: .625, and NPV: .7935). Moreover, all patients were divided into 4 groups based on the prevalence of nonparoxysmal AF and LV hypertrophy; Group A [n = 64, nonparoxysmal AF (-)/LV hypertrophy (-)], Group B [n = 16, nonparoxysmal AF (-)/LV hypertrophy (+)], Group C [n = 28, nonparoxysmal AF (+)/LV hypertrophy (-)], and Group D [n = 16, nonparoxysmal AF (+)/LV hypertrophy (+)]. The prevalence of LAT/SEC was 4.7%, 37.5%, 57.1%, and 87.5% in groups A, B, C, and D, respectively (Fig 3). The rate of LAT/SEC was the highest in group D.

Discussion

Main Findings

This is a retrospective study of the characteristics of patients with remaining LAT/SEC in the acute phase after the onset of CES using a single center database. Our study

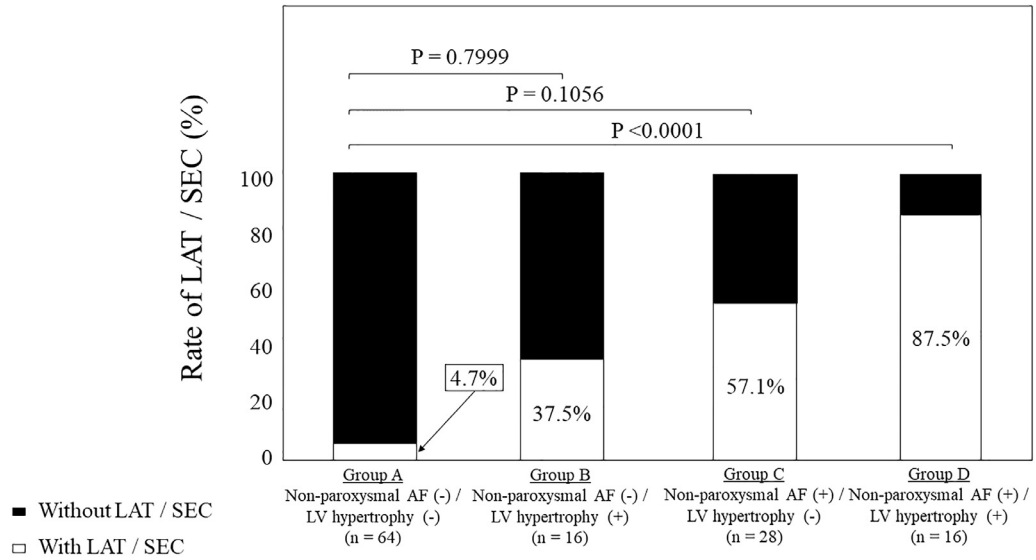

Figure 3. *Proportion of LAT/SEC in each combination of non-paroxysmal AF and LV hypertrophy. Abbreviations: AF, atrial fibrillation; LAT, left atrial thrombus; LV, left ventricular; SEC, spontaneous echo contrast.*

showed that LAT/SEC was associated with nonparoxysmal AF and LV hypertrophy on multivariate analysis. In contrast, the $CHADS_2$ and CHA_2DS_2-VASc scores were not associated with LAT/SEC. Moreover, all patients were divided into 4 groups based on the combination between nonparoxysmal AF and LV hypertrophy. The rate of LAT/SEC was the highest (87.5%) in group D [nonparoxysmal AF (+)/LV hypertrophy (+)].

Approximately 1 in 4 acute ischemic strokes can be attributed to an embolism that originates in the heart.[11] CES patients are likely to have a larger infarct volume and unfavorable outcomes than those with other stroke subtypes.[12] Furthermore, re-embolization occurs in 13%-20% of patients usually within 14 days of CES onset and adversely affects the patient`s prognosis.[13,14] Doi et al studied the prevalence of LAT after the onset of CES in 64 patients using TEE. They indicated that LAT was detected in 11/33 patients (33%) within 4 days of onset, and LAT was detected in 3/31 patients (10%) from 5 to 30 days after onset. Of these patients, lethal re-embolization occurred in 2 patients with highly mobile thrombi.[15] The following mechanisms of re-embolization have been considered; residual thrombi after stroke may be caused by fragments of a thrombus or multiple thrombi that float away to become the embolus; new thrombi may also develop in the left atrium because fibrinopeptide A levels are markedly elevated and thrombin is activated during the first week after stroke.[16] Regardless of mechanism, we believe that early detection of LAT/SEC and aggressive anticoagulant therapy is important to reduce the risk of the re-embolization due to residual LAT/SEC.

It is well known that LAT/SEC are high risk factors for CES. TEE is often performed for detection of LAT/SEC in patients with suspected CES. TEE provides high-quality images of cardiac structure and function, however, it is an invasive and costly procedure with the risk of complications such as trauma, vagal reactions or aspiration due to the probe insertion, allergic reactions to topical anesthesia, and hypotension or hypoxia due to conscious sedation.[17,18] Therefore, the decision to perform TEE after routine TTE in patients with acute ischemic stroke is controversial. Our findings showed that 87.5% patients with both non-paroxysmal AF and LV hypertrophy had LAT/SEC on TEE. These results suggest that performing a TTE is a sufficient screening modality for detecting LAT/SEC.

The $CHADS_2$ and CHA_2DS_2-VASc scores are useful for stratifying stroke risk in patients with nonvalvular AF and to identify patients that would benefit from anticoagulation. Moreover, the $CHADS_2$ and CHA_2DS_2-VASc scores are related to initial severity, as well as a 3-month outcome after stroke.[19,20] In our study, the $CHADS_2$ and CHA_2DS_2-VASc scores were not associated with residual LAT/SEC. Recently, Mascioli et al evaluated the performance of these traditional risk scores in identifying LAT/SEC in nonvalvular AF patients. They indicated that these scores were not able to identify patients with LAT/SEC at TEE.[21] Our results are in accordance with their findings. However, the mechanism of their findings remains unclear. The possible cause of these findings might be due to a variability of stroke causes. The traditional risk scores were made for stratifying all cause stroke including atherosclerotic cause. Our findings suggest that the prevalence of nonparoxysmal AF and LV hypertrophy are more useful for predicting LAT/SEC in patients with CES.

It is well known that thrombus formation is strongly associated with the pathophysiology of LA. However, previous studies on the association between stroke and type of AF have shown mixed results. Historically, the

risk of thromboembolism has been considered to be independent of AF type.[22,23] However, recent studies have reported that nonparoxysmal AF is associated with an increase in thromboembolism.[24,25] Inaba et al investigated the relationship between AF pattern (paroxysmal, persistent, or permanent AF) and the severity and brain volume of infarction in 161 patients with CES. They showed that persistent/permanent AF patients had worse NIHSS scores and larger infarct brain volumes.[26] Our findings are consistent with these recent reports indicating that nonparoxysmal AF is associated with LAT/SEC.

LV hypertrophy is a well-known risk factor for stroke, however, the exact mechanism underlying the residual LAT/SEC in LV hypertrophy patients has yet to be elucidated.[27,28] We considered the following mechanism of the relationship between LV hypertrophy and LAT/SEC. First, LV hypertrophy may increase the incident AF. Chrispin et al examined the association between LV hypertrophy and incident AF in 4942 patients without cardiovascular disease. They indicated that LV hypertrophy was associated with incident AF.[29] Second, increased LV diastolic filling pressure due to LV hypertrophy may induce a high LA pressure and result in thrombus formation in LA. A recent retrospective analysis of adults in the Cardiovascular Health Study (without stroke or AF) associated incident stroke with serum N-terminal pro-B-type natriuretic peptide (a marker of LA or LV wall stretch). Moreover, a recent study showed the lack of a temporal relationship between AF and embolic events.[30] In other words, they indicated that a direct cause of embolic events may not be AF itself but LA or LA appendage dysfunction. Their findings also indirectly suggest that LV hypertrophy may lead to LA thrombus formation even in the absence of AF.

LA diameter is well-known risk factor of LAT in AF patients. However, the results of our study showed that LA diameter was not associated with the LAT/SEC. Our results are different from previous results, and this discrepancy may be the results of different patient`s inclusion criteria such as the acute phase of CES. In other words, conventional risk factors of LAT, such as LA diameter, are useful for AF patients, not patients with the residual LAT/SEC in the acute phase of CES. Therefore, we consider that nonparoxysmal AF and LV hypertrophy are more useful for predicting the residual LAT/SEC in the acute phase of CES than the other conventional risk factors of intracardiac thrombus.

Clinical Implications

We found a higher prevalence of nonparoxysmal AF and LV hypertrophy in CES patients with LAT/SEC compared to those without LAT/SEC. Moreover, patients with both nonparoxysmal AF and LV hypertrophy had the highest prevalence of the LAT/SEC among the 4 groups. To the best of our knowledge, this is the first study to identify a relationship between LAT/SEC after CES onset and nonparoxysmal AF and LV hypertrophy. Consequently, the assessment of these factors may have a critical implication in risk stratification of CES. Our results suggest that patients with nonparoxysmal AF, particularly those with LV hypertrophy, have a higher risk of re-embolization. We believe that early detection of LAT/SEC and aggressive anticoagulant therapies are important to reduce re-embolization risk due to residual LAT/SEC. However, data on residual LAT/SEC after CES onset are limited and further investigation will be necessary.

Study Limitations

There were several limitations to our study. First, this is a retrospective observational study with a small number of patients in a single center. Second, our study might include other types of stroke including atherosclerotic cause. In our study, CES patients were diagnosed by a stroke neurologist. However, in some cases, it is difficult to determine CES. Third, in some cases, LAT might float away from the LA at the time of CES. In our study, all patients with LAT had SEC. Therefore, the LAT/SEC group included mostly high-risk patients. Fourth, this study focused on a selected group of the acute CES patients in order to exclude the other types of stroke as much as possible. Fifth, there were small number of patients with structural heart disease in our study. This factor might be important factor for LAT/SEC. Therefore, further investigation will be necessary. Finally, anticoagulant therapy might impact the prevalence of LAT. A few LAT might disappear with anticoagulation therapy after CES onset.

Conclusions

Nonparoxysmal atrial fibrillation and left ventricular hypertrophy were associated with residual left atrial thrombus/spontaneous echo contrast after the onset of cardioembolic stroke that was independent of the $CHADS_2$ and CHA_2DS_2-VASc scores.

Supplementary Materials

Supplementary data to this article can be found online doi: https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.03.003.

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