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Association between Mobility of Residual Left Atrial Thrombus and Stroke Severity in Patients with Nonvalvular Atrial Fibrillation

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Background: The differences in the characteristics of ischemic stroke associated with a mobile versus nonmobile residual left atrial thrombus (LAT) are unclear. We investigated whether the mobility of an LAT detected by transthoracic echocardiography is associated with the clinical features of stroke.

Methods: This study included 20 consecutive patients with nonvalvular atrial fibrillation who were admitted to our hospital for treatment of acute ischemic stroke and then found to have an LAT on transthoracic echocardiography. The patients were divided into two groups: those with a mobile LAT (Group M) and those with a nonmobile LAT (Group N). The clinical, neuroradiological, and echocardiographic variables were assessed.

Results: The LAT was mobile in 11 patients (Group M) and nonmobile in nine patients (Group N). The median National Institutes of Health Stroke Scale score on admission was higher in Group M than N (17 vs. 7, respectively; p=0.196). Four patients in Group M and one in Group N developed in-hospital stroke recurrence (36% vs. 11%, respectively; p=0.319). The prevalence of large vessel occlusion (15 events in Group M and 10 events in Group N, including in-hospital recurrent events) was significantly higher in Group M than N (73% vs. 30%, respectively; p=0.049), which seemed to lead to poorer functional outcomes in Group M than N (ratio of modified Rankin scale score of 0-2 at discharge: 18% vs. 44%, respectively; p=0.336).

Conclusions: The mobility of LAT may affect stroke severity in patients with nonvalvular atrial fibrillation. (J Nippon Med Sch 2024; 91: 322–327)

Key words: cardioembolic stroke, left atrial thrombus, transthoracic echocardiography

Introduction

Rapid and ineffective contraction of the left atrium (LA) in patients with nonvalvular atrial fibrillation (NVAF) causes blood stasis, which can eventually result in thrombus formation. An LA thrombus (LAT) is believed to be the primary source of systematic embolism in patients with NVAF[1]. An LAT can be mobile or nonmobile, but the differences in the characteristics of the stroke caused by each type of LAT are unclear. The mobility of the thrombus should reflect the pathophysiology in the LA and may be related to the clinical features of stroke. However, few reports have focused on the relationship between the mobility of an LAT and stroke characteristics.

Transthoracic echocardiography (TTE) is a minimally invasive imaging technique that is widely used for screening of LAT in patients with stroke, although it is less sensitive than transesophageal echocardiography (TEE)[2,3]. In this study, we investigated whether the mobility of an LAT detected by TTE is associated with clinical symptoms of NVAF-associated acute ischemic stroke.

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Materials and Methods

This retrospective study was approved by the Institutional Review Board of Saitama Medical University International Medical Center (approval number: 20-095). Patients were not required to give informed consent to participate in the study because the analysis used anonymous clinical data that were obtained after each patient had provided written consent for treatment. Further, we applied an opt-out method to obtain consent for this study through an announcement on our hospital's website. The announcement was approved by the institutional review board.

This study included 20 consecutive patients with NVAF who were admitted to our hospital for acute ischemic stroke and then found to have an LAT on TTE from April 2007 (when the hospital opened) to May 2020. NVAF was defined as the presence of atrial fibrillation without mitral valve disease (mitral valve stenosis) or artificial valve replacement[4].

We retrospectively analyzed the clinical data of patients who had NVAF-associated acute ischemic stroke with an LAT. Acute ischemic stroke was defined as hospital arrival within 7 days of symptom onset. The data were obtained from electronic medical charts and summaries. We evaluated the patients' characteristics (age and sex), NVAF subtype (paroxysmal or persistent), underlying risk factors for stroke (hypertension, diabetes mellitus, dyslipidemia, current smoking, prior stroke, coronary artery disease, and congestive heart failure), echocardiographic findings, laboratory data (D-dimer concentration, brain natriuretic peptide concentration, and creatinine clearance) on admission, and use of antithrombotic (antiplatelet and/or anticoagulant) agents before the index stroke.

We also evaluated the National Institutes of Health Stroke Scale (NIHSS) score, brain computed tomography and magnetic resonance imaging/magnetic resonance angiography, recanalization therapies (thrombolysis and/or thrombectomy), anticoagulant medications after stroke, functional outcome using the modified Rankin scale score at discharge[5], and the duration of hospital stay. Brain computed tomography and/or magnetic resonance imaging was used to identify the infarct in all patients, and the infarct size was defined as follows: small, longest diameter $\leq$ 15 mm; large, larger than one-third of the territory of the middle cerebral artery, anterior cerebral artery, posterior cerebral artery, or cerebellar hemisphere; and medium, all other sizes[6]. Large vessels were defined as the internal carotid artery, the proximal portion of the middle cerebral artery (M1 segment), and the basilar artery.

TTE was performed within an average of 1 week of admission in both groups. Two cardiologists who were blinded to the stroke characteristics reviewed all TTE studies and assessed the mobility and size of each LAT. Thrombi that were mural or sessile with no pedunculated or mobile components were considered nonmobile, whereas pedunculated thrombi or thrombi with mobile components were considered mobile[7]. The maximum dimensions (in any plane) of the thrombi were measured. The patients were divided into two groups: those with a mobile LAT (Group M) and those with a nonmobile LAT (Group N). The therapeutic strategies did not differ between the groups.

Statistical analysis was performed using PASW statistical software version 20 (IBM Corp., Armonk, NY, USA). The Mann-Whitney U test and Fisher's exact test were used to compare the characteristics between the groups. A p value of <0.05 was considered statistically significant.

Results

An LAT was detected by TTE in 20 (1.5%) of 1,303 patients with NVAF-associated acute ischemic stroke. The thrombus was mobile in 11 patients (Group M) and nonmobile in 9 patients (Group N). The background characteristics of the patients in each group are listed in **Table 1**. The $CHADS_2$ and $CHADS_2$-VASc scores did not differ significantly between the two groups. The stroke characteristics in each group are listed in **Table 2**. There were 15 events in Group M and 10 events in Group N, including in-hospital recurrent events. The prevalence of large vessel occlusion (LVO) was significantly higher in Group M than in Group N (73% vs. 30%, respectively; p=0.049). However, the median NIHSS score did not differ significantly between Group M and Group N (17 vs 7, respectively; p=0.196). Four in-hospital stroke recurrences occurred in Group M (mean, day 9) and one occurred in Group N (day 3) (36% vs. 11%, respectively; p=0.319), and all but one case in Group M resulted in death or a bedridden state due to LVO. Two patients in Group M developed stroke recurrence under effective anticoagulant therapy, and the others developed stroke recurrence in the absence of anticoagulant therapy. The treatment used in each group is listed in **Table 3**. There was no difference in effective anticoagulant therapy before stroke onset, from stroke onset to TTE, and after TTE between two groups. The ratio of good outcomes (modified Rankin scale score of 0-2) was not significantly different

Table 1 Background characteristics of patients with residual left atrial thrombus

Characteristics	Group M (n=11)	Group N (n=9)	*p* value
Age, years	75.9 ± 11.2	76.6 ± 8.8	0.909
Female sex	8 (73)	4 (44)	0.362
Body weight, kg	50.0 ± 10.9	60.9 ± 16.3	0.128
BMI, kg/m^2	20.9 ± 3.4	22.8 ± 4.9	0.305
NVAF subtype			0.362
paroxysmal	3 (27)	5 (56)	
persistent	8 (73)	4 (44)	
Risk factors			
Hypertension	10 (91)	7 (78)	0.285
Diabetes mellitus	1 (9)	2 (11)	0.566
Dyslipidemia	5 (45)	1 (11)	0.157
Current smoking	1 (9)	0 (0)	1.000
Prior stroke	4 (36)	6 (67)	0.370
CAD	2 (18)	0 (0)	0.479
Congestive heart failure	4 (36)	2 (22)	0.642
$CHADS_2$ score	3 [2–3.5]	3 [2–4]	0.525
CHA_2DS_2-VASc score	5 [4–6]	4 [4–6]	0.726
HAS-BLED score	2 [4–6]	3 [4–6]	0.200
Antithrombotic drug			
Antiplatelet drugs	2 (18)	4 (44)	0.336
Warfarin	2 (18)	1 (11)	1.000
DOAC	3 (27)	1 (11)	0.591

Data are shown as mean ± standard deviation, n (%), or median [interquartile range].
Abbreviations: NVAF, nonvalvular atrial fibrillation; BMI, body mass index; DOAC, direct oral anticoagulant; CAD, coronary artery disease

between Group M and Group N (18% vs 44%, respectively; p=0.336).

The echocardiographic findings in each group are listed in **Table 4**. There were no significant differences between the groups. Four patients (2 in Group M, 2 in Group N) underwent TEE after TTE and were found to have LAT. Follow-up TTE confirmed resolution of LAT in 9 patients (5 in Group M, 4 in Group N) and reduction of LAT in 3 cases (2 in Group M, 1 in Group N). Eight patients (4 in Group M, 4 in Group N) did not undergo follow-up TTE.

Discussion

In the present study, TTE showed an LAT in 1.5% of patients with acute ischemic stroke with NVAF. Approximately half of the patients had a mobile LAT, which was associated with LVO. Although not statistically significant, stroke with a mobile LAT tended to be associated with poorer functional outcomes than stroke with a nonmobile LAT. Therefore, we speculate that the thrombus size that caused stroke was larger in Group M than in Group N, although the residual LAT size found on TTE was not different. Because a mobile thrombus is considered to be fresher and more fragile than a nonmobile thrombus, we speculate that ongoing thrombus formation and growth were occurring in Group M.

In the present study, three patients with recurrent stroke in Group M developed LVO that resulted in death or a bedridden state. Doi et al.[8] studied the prevalence of LAT after cardioembolic stroke using TEE and similarly reported two cases of recurrent stroke associated with highly mobile thrombi that resulted in death. Although early anticoagulation therapy in patients with NVAF-associated acute ischemic stroke occasionally leads to hemorrhagic transformation, aggressive anticoagulant therapy may be considered to reduce the risk of recurrence, especially in patients with a mobile LAT.

Several studies have demonstrated that TEE is superior to TTE for detection of LAT in patients with stroke[3,9]. Tanaka et al.[3] found a thrombus in 7.8% of patients using TEE but in only 0.6% using TTE. We detected an LAT in 1.5% of patients with NVAF-associated stroke. The reason

Table 2 Stroke characteristics of patients with residual left atrial thrombus

Characteristics	Group M (n=11)	Group N (n=9)	*p* value
NIHSS score on admission	17 [11.5–27]	7 [3–16]	0.196
In-hospital stroke recurrence	4 (36)	1 (11)	0.319
Large artery occlusion*	11 (73)	3 (30)	0.049
ICA	2	1	
MCA M1	8	1	
BA	1	1	
Stroke size*			0.491
Large	9 (60)	4 (40)	
Middle	5 (33)	4 (40)	
Small	1 (7)	2 (20)	
Laboratory data on admission			
D-dimer, μg/mL	3.0 ± 3.5	2.4 ± 1.6	0.901
BNP, pg/mL	503 ± 377	351 ± 370	0.346
Creatinine clearance, mL/min	54 ± 22	75 ± 32	0.254
Hospital stay, days	28 ± 16	29 ± 14	0.909
Outcomes			
mRS score at discharge	5 [4–6]	5 [2–6]	0.905
mRS score 0–2 at discharge	2 (18)	4 (44)	0.336
Mortality	4 (36)	4 (44)	1.000

*There were 15 events in group M and 10 events in group N, including in-hospital recurrent events.
Data are shown as median [interquartile range], n (%), or mean ± standard deviation.
Abbreviations: NIHSS, National Institutes of Health Stroke Scale; ICA, internal carotid artery; MCA, middle cerebral artery; BA, basilar artery; mRS, modified Rankin scale

Table 3 Treatment for patients with residual left atrial thrombus

Characteristics	Group M (n=11)	Group N (n=9)	*p* value
Recanalization therapies			0.218
thrombolysis	0 (0)	0 (0)	
thrombectomy	3 (27)	0 (0)	
Effective anticoagulant therapy			
Before stroke onset	6 (55)	2 (22)	0.197
Before TTE	6 (55)	3 (33)	0.410
After TTE	10 (91)	6 (66)	0.285
Secondary prevention			
Warfarin only	5 (46)	2 (22)	
Heparin only*	2 (18)	1 (11)	
Heparin before warfarin	2 (18)	3 (33)	
Heparin before DOAC	1 (9)	0 (0)	
No anticoagulants	1 (9)	3 (33)	

*Two patients (1 in Group M and 1 in Group N) died while receiving heparin, one due to heart failure and the other due to cerebellar hemorrhage. One patient (Group M) was transferred for endoscopic left atrial appendectomy under heparin.
Data are shown as n (%).
Abbreviations: TTE, transthoracic echocardiography; DOAC, direct oral anticoagulant

Table 4 Echocardiographic findings of patients with residual left atrial thrombus

Characteristics	Group M (n=11)	Group N (n=9)	*p* value
Days from admission to examination	4.1 ± 2.3	3.4 ± 1.7	0.562
Thrombus size			
Long diameter, mm	24 ± 9	25 ± 8	0.869
Short diameter, mm	14 ± 6	12 ± 7	0.431
Area, mm^2	375 ± 273	331 ± 260	0.563
Left atrial dimension, mm	47 ± 8	50 ± 10	0.790
Ejection fraction, %	54 ± 14	61 ± 19	0.447

Data are shown as mean ± standard deviation.

for the difference in sensitivity is not clear, but it may indicate that TTE is not the most accurate method for LAT detection. However, it is not easy for patients with acute stroke to undergo TEE. Thus, it is important to clarify the relationship between the mobility of LAT detected with TTE and stroke characteristics.

The present study showed no differences in background characteristics between the two groups. It is well known that thrombus formation is strongly associated with pathophysiology in the LA. Mascioli et al.[10] found that the $CHADS_2$ and CHA_2DS_2-VASc scores were not useful in identifying LAT in patients with NVAF. Likewise, our study showed that the $CHADS_2$ and CHA_2DS_2-VASc scores did not predict LAT detection.

Our study had several limitations. First, this was a retrospective observational study with a small number of patients in a single center. Second, this study focused on a select group of patients with acute NVAF-associated ischemic stroke to clarify the significance of thrombus mobility. Third, TTE does not always provide a suitable window for observing the LA appendage, and thrombi identified by TTE alone might represent false-positive results[2]. Finally, anticoagulation therapy might impact the prevalence of LAT. Some LATs might disappear with anticoagulation therapy after stroke.

Among patients with NVAF-associated acute ischemic stroke with an LAT detected by TTE, a mobile LAT was associated with a significantly higher prevalence of LVO than a nonmobile LAT and seemed to lead to poorer functional outcomes than a nonmobile LAT. Furfur large-scale study is necessary to determine how the mobility of LAT affects stroke severity.

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Conflict of Interest: None.

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