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【 ORIGINAL ARTICLE 】

Features of Cerebral Infarction Due to Left Ventricular Thrombus

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Abstract:

Objective Left ventricular (LV) thrombus is a rare condition in acute cerebral infarction. The prevalence and features of cerebral infarction with LV thrombus are unclear. We explored the features of cerebral infarction due to LV thrombus.

Methods In this single-center retrospective study, we investigated consecutive patients with acute ischemic stroke admitted within seven days of the onset who had LV thrombus found by transthoracic echocardiography (TTE). First, we calculated the prevalence of LV thrombus in patients with cardioembolic stroke (CES). Second, we investigated the baseline characteristics, including the TTE findings and features of cerebral infarction due to LV thrombus.

Results From June 2012 to January 2019, a total of 5,693 patients were enrolled. Of these, 1,408 (25%) patients were diagnosed with CES. Of these 1,408 patients with CES, 13 (0.9%) had LV thrombus indicated by TTE, with dilative cardiomyopathy, subacute myocardial infarction, and old myocardial infarction present in 1 (8%), 2 (15%), and 10 (77%), respectively. The ejection fraction (EF) was 48.9% (25.3-64.7%). The maximum longitudinal size of LV thrombus was 13.4 (0.97-38.1) mm, and there was no correlation between the size of the LV thrombus and the EF. Regarding the features of cerebrovascular infarction, major vessel occlusion was observed in 10 (77%) patients. Six (46%) patients were found to have good outcomes (modified Rankin Scale 0-2) at 90 days after the onset.

Conclusion LV thrombus was seen in 0.9% of patients with CES. Many of the patients with LV thrombus had major vessel occlusion.

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

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Introduction

Left ventricular (LV) thrombus is considered rare, even after myocardial infarction (MI) (1). In stroke treatment, the term 'intracardiac thrombus' generally refers to a thrombus in the left atrial appendage due to atrial fibrillation. As LV thrombus is very rare in acute stroke patients, the prevalence and features of cerebral infarction with LV thrombus are unclear.

In the present study, we explored the features of cerebral infarction due to LV thrombus.

Materials and Methods

Study protocol

This was a single-center retrospective study. We investigated consecutive acute ischemic stroke patients admitted to our stroke center within seven days of the onset. In our stroke center, we evaluated all patients using the TOAST criteria, so transthoracic echocardiography (TTE) was performed within two days after admission, or if needed, on the day of admission. In this study, we focused on the TTE findings and selected patients with thrombus in the LV.

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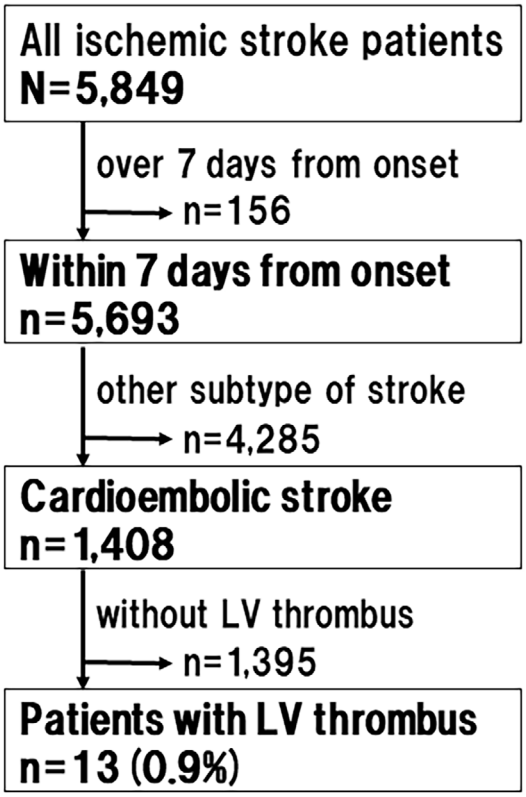

Figure 1. Patient selection criteria. Of the 5,849 patients with cerebral infarction, 5,693 were admitted within 7 days of the onset. Cardioembolic stroke was observed in 1,408 (26%) patients. Of these 1,408 patients, 13 (0.9%) had left ventricular thrombus.

We first calculated the prevalence rate of LV thrombus in patients with acute ischemic stroke within seven days of the onset and in patients with cardioembolic stroke (CES) in the same period. We then compared the clinical features, such as risk factors, basal cardiovascular disease, TTE findings, magnetic resonance imaging (MRI) features of cerebral infarction, neurological symptoms using the National Institutes of Health Stroke Scale, and prognosis using the modified Rankin Scale (mRS) between CES due to LV thrombus and other CES patients. We also compared the laboratory data between the two groups but were only able to collect data after April 2016 because of our system.

TTE protocol

A Philips IE33 color Doppler ultrasonic diagnostic system (Philips Medical Systems, Andover, USA) with a 3.0-MHz probe was used in our center. TTE was performed by a well-trained medical technician who had worked at our hospital for over five years, and the findings were double-checked by a cardiologist offline.

Statistical analyses

A univariate analysis was performed using Fisher's exact test and the Mann-Whitney U test. The SPSS software program, version 24.0 (Statistical Package for the Social Sciences, IBM, Armonk, USA), was used for the statistical analysis. A p-value of <0.05 was considered statistically significant. The correlation between the size of LV thrombus and the ejection fraction (EF) was assessed using Spearman's rank correlation coefficient.

This study was performed in accordance with the guidelines of the Ethics Committee of the Brain Attack Center Ota Memorial Hospital.

Results

From June 2012 to January 2019, 5,849 patients with ischemic stroke were admitted to our hospital. Of these, 5,693 were admitted within 7 days of the onset. We performed TTE for all patients, and 13 had LV thrombus (0.23%). As CES was observed in 1,408 (25%) patients, 0.9% of CES patients had LV thrombus (Fig. 1).

Table shows the basal characteristics of the patients with LV thrombus and other CES patients, including the MRI findings and laboratory examination results. The patients with LV thrombus were much younger than the other CES patients (66 vs. 81 years old, $p<0.001$) and more frequently men (92% vs. 50%, $p=0.002$). Regarding the basal cardiovascular disease of the patients with LV thrombus, dilative cardiomyopathy, subacute MI, and old MI (OMI) were observed in 1 (8%), 2 (15%), and 10 (77%) patients, respectively. Of the 10 patients with OMI, 5 had been diagnosed before, and 5 had been diagnosed for the first time. Three of the five patients who had been diagnosed before stopped taking medicine by themselves, and the other two had received single antiplatelet therapy. The time from OMI to the onset of cerebral infarction was a median 10 years (range 7-37 years). The EF was 48.9% (25.3-64.7%), which was lower than that of other patients with CES (62.9%, $p<0.001$). The maximum longitudinal size of LV thrombus was 13.4 (0.97-38.1) mm, and there was no correlation between the size of LV thrombus and EF (Fig. 2).

Regarding the features of cerebrovascular infarction, major vessel occlusion was observed in 10 (77%) patients, which was more than in the other CES patients (38%, $p=0.007$) (Table). Intravenous recombinant tissue-type plasminogen activator (rt-PA) therapy was performed in only one patient, and intra-arterial thrombectomy was performed in three patients. All patients received intravenous heparin and oral vitamin K antagonist. Six (46%) patients' condition worsened (n=1) or relapsed (n=5) after starting treatment. The median period from starting treatment to recurrence was 7 days (range 2-10 days). Two patients underwent surgery for thrombus removal during the acute phase and did not relapse. Six (46%) patients were found to have good outcomes (mRS 0-2) at 90 days after the onset.

Discussion

We herein report the features and prognosis of cerebral infarction from LV thrombus found by TTE. The main features were as follows: 1) the proportion of cardioembolic

Table. The Basal Characteristics of the Patients with LV Thrombus and Other CES Patients.

Characteristics	With LV thrombus n=13	The other CES n=1,395	p value
Age, yr, median (IQR)	66 (59-75)	81 (72-87)	<0.001
Male sex, n (%)	12 (92.3)	697 (50.0)	0.002
Medical history, n (%)			
Hypertension	11 (84.6)	1,111 (79.6)	1.000
Diabetes mellitus	4 (30.7)	387 (27.3)	0.759
Dyslipidemia	9 (69.2)	613 (43.9)	0.068
Atrial fibrillation	4 (30.7)	970 (69.5)	0.005
Current smoking	3 (23.1)	186 (13.3)	0.401
Initial NIHSS, median (IQR)	7 (1-20)	7 (2-19)	0.562
BNP (pg/mL), median (IQR)	95.3 (30.5-278.7)	165.8 (75.7-314.5)*	0.119
D-dimer (μg/mL), median (IQR)	1.8 (1.2-4.9)	1.5 (0.9-2.9)*	0.300
Basal cardiovascular disease, n (%)			
Old myocardial infarct	10 (76.9)	155 (11.1)	<0.001
Subacute phase myocardial infarct	2 (15.4)		
Dilated cardiomyopathy	1 (7.7)		
Transthoracic echocardiography findings			
Ejection franction (%), median (IQR)	48.9 (25.3-64.7)	64.4 (59.4-70.0)	<0.001
Greatest dimension of thrombus (mm), median (IQR)	13.4 (0.97-38.1)		
Ventricular aneurysm, n (%)	1 (7.7)		
Mobile thrombus, n (%)	2 (15.4)		
MRI fingings			
Major vessel occlusion	10 (76.9)	530 (38.0)	0.007
Site of occluded artery:IC/M1/M2/VA/BA	3/1/3/2/1	128/186/30/186	
Treatment			
rt-PA	1 (7.7)	174 (12.5)	1.000
Endovascular treatment	4 (30.7)	257 (18.4)	0.277
Operation (thrombectomy)	1 (7.7)		
modified Rankin Scale 0-2 at discharge, n (%)	6 (46.2)	597 (42.8)	0.809

Data are presented as the median (IQR) or number (%) of patients.

LV: left ventricular, CES: cardioembolic stroke, IQR: interquartile range, NIHSS: National Institutes of Health Stroke Scale, BNP: brain natriuretic protein, MRI: magnetic resonance imaging, rt-PA: recombinant tissue-type plasminogen activator, *n=544

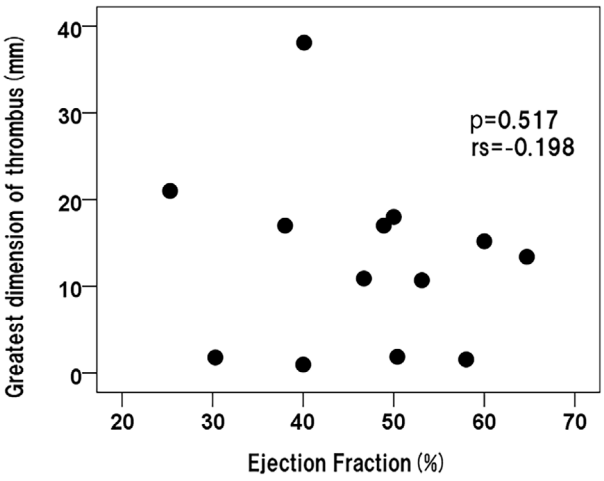

Figure 2. Relationship between left ventricular (LV) thrombus size and the ejection fraction (EF). There was no correlation between the LV thrombus size and the EF.

stroke with LV thrombus was 0.9% of consecutive CES, 2) OMI was more frequent than subacute MI with regard to basal cardiovascular disease, and 3) almost half of the patients' conditions worsened or relapsed after starting treatment.

LV thrombus is considered rare even after MI, with its prevalence being previously reported as 2.7% after all MI and 9.1% after anterior MI (1). However, recently, the incidence of LV thrombus has been reported to have increased to 19.2% when only anterior MI with LVEF <50% was considered (2). Bulluck et al. also reported that 88% of LV thrombi disappeared by 3 to 6 months without any embolic episode, and the embolic complication rate was 1.5% after a 1- to 2-year follow-up period. In our cohort, the patients with OMI had cerebral infarction due to LV thrombus more frequently than those with acute MI, and half of the OMI patients were first recognized as having OMI. Three of the five known OMI patients with cerebral infarction interrupted their medication by themselves. Including unknown OMI patients, 8 of 10 (80%) patients had no medication, including anticoagulation and antiplatelet therapy. We consider it important to take suitable medication in order to avoid embolic episodes after MI.

The incidence rate of LV thrombus in consecutive

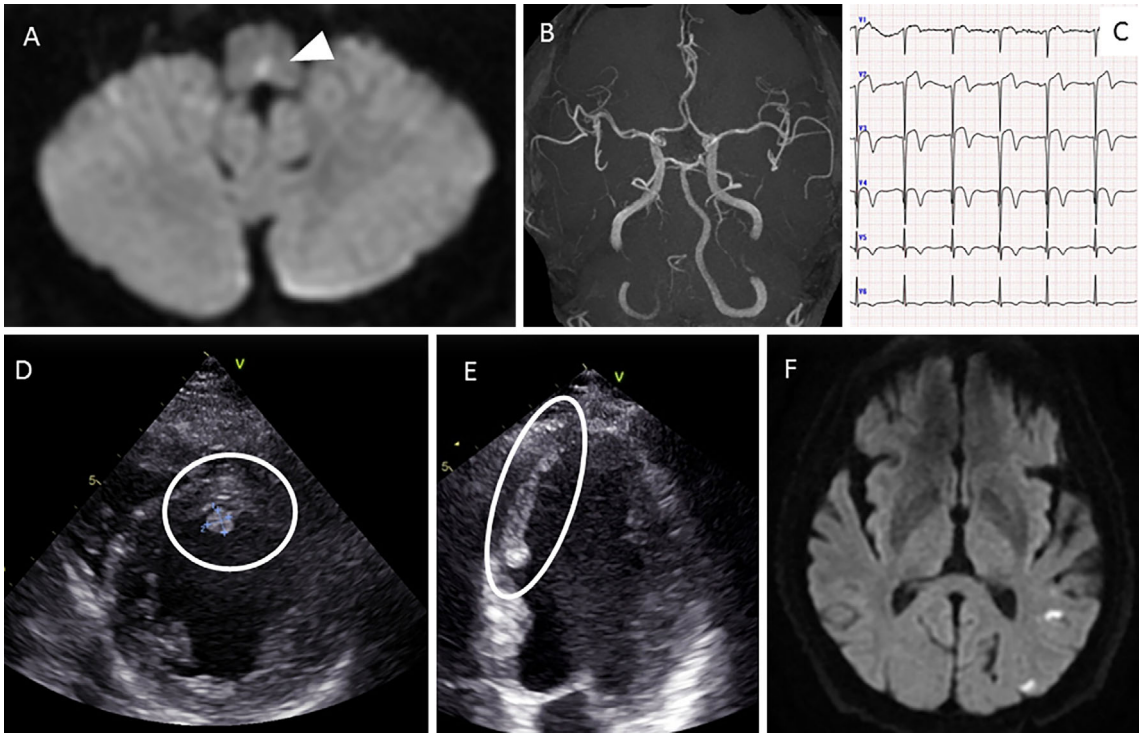

Figure 3. **Representative case with left ventricular thrombus. A 60-year-old man was admitted to our hospital with dysarthria and dizziness. Magnetic resonance imaging (MRI) showed cerebral infarction at the medulla (A) and right vertebral artery occlusion on MR angiography (B). He had no history of myocardial infarction, but an electrocardiogram showed ST elevation and a negative T wave from V1 to V4 (C). The echocardiogram revealed left ventricular dysfunction (EF, 55%) and thrombus (D, E). His symptoms worsened six hours after treatment with heparin, and MRI showed recurrence of cerebral infarction (F).**

ischemic stroke patients remains unclear, and to our knowledge, this is the first report to indicate this. In this study, we investigated LV thrombus only with TTE. Takasugi et al. reported that LV thrombus was confirmed in 12 patients on contrast-enhanced cardiac MRI, whereas only 1 case was detected on TTE (p=0.04) in 178 patients with embolic stroke of undetermined source (3). Therefore, the incidence rate of LV thrombus might have been higher in the current study if we had used MRI as well as TTE.

When LV thrombus is detected, anticoagulation therapy is essential. In our cohort, approximately one third of patients relapsed after starting treatment, with this often happening within seven days after the initiation of intravenous heparin (Fig. 3 shows representative case). Therefore, patients should be carefully monitored after starting treatment. Within several days after starting intravenous heparin, we usually change out oral vitamin K antagonists (VKAs) to prevent subsequent stroke or systemic thromboembolism. Direct oral anticoagulants (DOACs) have no indications for LV thrombus in Japan and the efficacy and safety of DOAC use for LV thrombus remain controversial. One multicenter cohort study regarding LV thrombus reported that DOAC treatment (Off-label use) was associated with a higher risk of stroke or systemic embolism than VKAs (4). However, a recent meta-analysis concluded that there were no significant differences between VKAs and DOACs (5-7). A systematic review and meta-analysis concerning the efficacy and safety of DOACs in the treatment of LV thrombus by Burmeister et al. revealed that the LVT resolution was significantly higher in DOACs than in VKAs [relative risk (RR): 1.18, p=0.01] (5). Kitano et al. reported there were no significant differences between VKAs and DOACs in the frequency of thrombus resolusion, stroke, any thromboembolism, major bleeding, and all cause death (6). Kido et al. also concluded by a meta-analysis that DOACs may be feasible alternative anticoagulants to VKAs (7). Unfortunately, as DOACs have no indication for LV thrombus in Japan, we must use VKAs at present. The accumulation of more evidence is needed in order to conclude the efficacy and safety of DOAC use.

No study has evaluated the treatment of acute ischemic stroke patients with LV thrombus. We treated one patient with t-PA and three with intraarterial thrombectomy. Although there was no relapse during our procedure, whether or not small clots can dislodge and create another systemic thromboembolism when t-PA dissolves thrombus in the LV remains controversial. More systemic studies are needed to clarify the efficacy and safety of each treatment for acute ischemic stroke due to LV thrombus.

Several limitations associated with the present study warrant mention. First, this was a single-center cohort and retrospective study. Second, as there were only 13 patients with LV thrombus, the features of baseline characteristics and

cerebral infarction could easily have fluctuated.

In conclusion, acute cerebral infarction due to LV thrombus detected by TTE was rare, occurring in 0.9% of consecutive CES patients, but the recurrence rate in the acute phase after starting treatment was high. We should recognize LV thrombus as a cause of cardioembolic stroke that requires attention.

The authors state that they have no Conflict of Interest (COI).

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