

[ ORIGINAL ARTICLE ]

## Diagnostic Yield of Early Examination for Venous Thrombosis in Patients with Cryptogenic Stroke and a Right-to-left Shunt

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### Abstract:

**Objective** The presence of deep venous thrombosis (DVT) in a cryptogenic stroke (CS) patient with a right-to-left shunt (RLS) may lead to the development of paradoxical embolism. The aim of the present was to investigate the prevalence of DVT and pulmonary embolism (PE) in CS patients and the clinical features of CS in relation to DVT location and the presence of PE.

**Methods** The medical records of 903 patients with cerebral infarction were retrospectively reviewed. For patients with a diagnosis of CS, contrast saline transcranial color-coded sonography was performed to identify an RLS. DVT and PE were assessed by duplex ultrasonography and/or contrast-enhanced computed tomography. Proximal DVT (P-DVT) was defined as DVT in the popliteal, femoral, or iliac veins, and distal DVT (D-DVT) was defined as DVT at other locations. The patients were divided into three groups: CS with P-DVT and/or PE (P-DVT/PE) group; CS with D-DVT (D-DVT) group; and CS without DVT (no DVT) group.

**Results** Seventy-two (37%) of 194 patients with CS had an RLS. The median time to first DVT examination from stroke onset was three days. Twenty-nine percent of CS patients with an RLS had DVT. The P-DVT/PE group comprised 8.3% of the CS patients with an RLS and included a larger number of patients with multi-territory infarction than the D-DVT group. The D-DVT and P-DVT/PE groups tended to be female and older, while the P-DVT/PE group tended to have pre-stroke disability.

**Conclusion** CS patients, especially those with multi-territory lesions, should be immediately examined for DVT and PE.

**Key words:** cryptogenic stroke, right-to-left shunt, patent foramen ovale, deep venous thrombosis, pulmonary embolism

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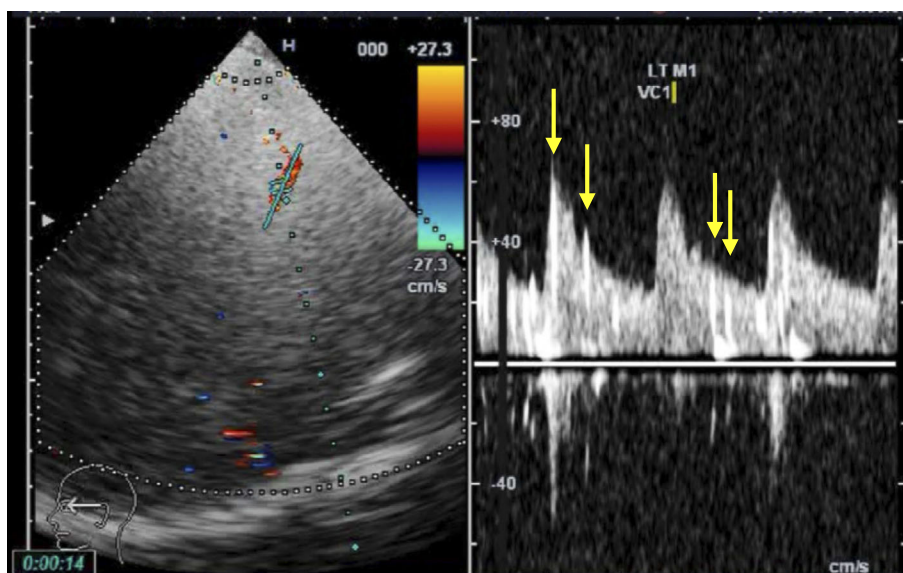
### Introduction

Deep vein thrombosis (DVT) is not uncommon in ischemic stroke patients. In particular, the presence of DVT in cryptogenic stroke (CS) patients with a right-to-left shunt (RLS) may lead to the development of paradoxical embolism, and DVT should be more carefully managed in such cases.

In general practice, the treatment approaches to DVT de-

pend on the location of the DVT [distal DVT (D-DVT) or proximal DVT (P-DVT)] and the presence of pulmonary embolism (PE). The risk of proximal extension of untreated D-DVT is 20% (1), and serial imaging follow-up can be appropriate if the thrombus does not extend in patients with D-DVT. Needless to say, P-DVT or PE should be strictly managed with anticoagulation. However, in CS patients with an RLS, it is still uncertain how to manage DVT in relation to the location of DVT and the presence of PE. If CS patients have P-DVT and/or PE, immediate anticoagulation might

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**Figure 1.** Investigation of right-to-left shunt by contrast saline transcranial color-coded sonography (TCCS). TCCS can visualize the flow of the middle cerebral artery through the temporal bone window (left). When short-duration and high intensity signals were observed (arrows), we confirmed the presence of right-to-left shunt (right).

contribute to the prevention of stroke recurrence. The aim of the present study was to investigate the prevalence of DVT and PE in CS patients and the clinical features of CS in relation to the location of DVT and the presence of PE.

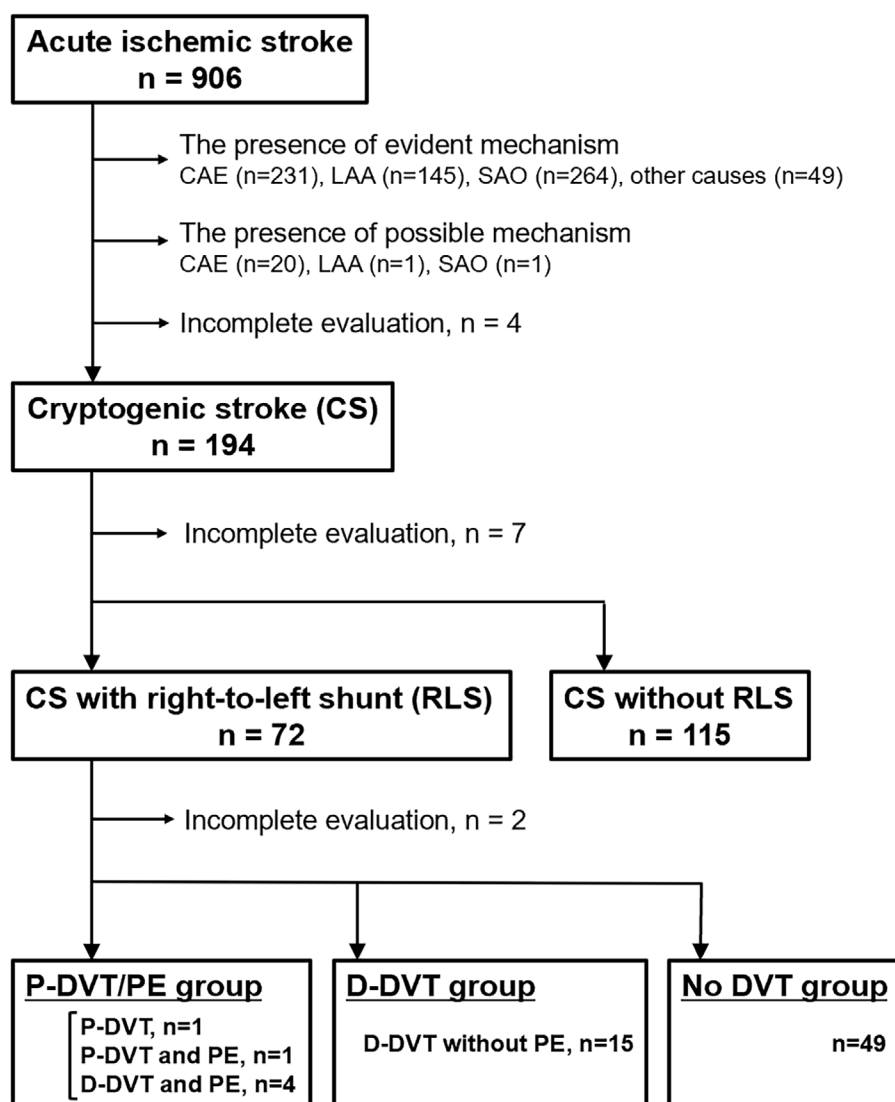
## Materials and Methods

The medical records of patients with acute cerebral infarction within 7 days of stroke onset from November 2012 to July 2018 were reviewed retrospectively. Cerebral infarction was diagnosed using diffusion-weighted imaging (DWI) within 24 hours after admission. The criteria for the diagnosis of CS were established as: [1] lack of cardioaortic sources of stroke other than the patent foramen ovale (PFO); [2] lack of arterial disease with >50% stenosis in the affected artery; [3] lack of imaging evidence of a single infarction of <20 mm in greatest diameter within the basal or brainstem territory; and [4] lack of other causes, including arterial dissection, cerebral venous thrombosis, hereditary syndromes [e.g., cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)], and iatrogenic causes (e.g., endovascular interventions and cardiac or arterial surgery) that were defined as unknown cryptogenic embolism or other cryptogenic stroke by the Causative Classification of Stroke (CCS) system (2). All patients diagnosed with CS underwent carotid duplex ultrasound, magnetic resonance angiography, transthoracic echocardiography and 24-hour Holter electrocardiography (ECG). Transesophageal echocardiography (TEE) was performed in selected patients. In comparison to the criteria for embolic stroke of undetermined source (3), low-risk sources of embolism (e.g., aortic-arch atherosclerosis or mild left ventricular dysfunction) were considered as possible etiolo-

gies of stroke in the present study.

The following clinical characteristics of the patients were evaluated: [1] age, sex; [2] stroke risk factors (including hypertension, dyslipidemia, diabetes mellitus, family history of stroke, smoking, past history of stroke); [3] National Institutes of Health Stroke Scale (NIHSS) score on admission and discharge, the modified Rankin scale score before the onset of stroke and three months after stroke; [4] D-dimer levels; and [5] the time from stroke onset to the first DVT examination. MRI/MR angiography was performed twice after admission. In order to diagnose cerebral embolism, medical records and MRI/MR angiography were fully reviewed to identify the following features: [1] sudden symptom onset; [2] recanalization of an occluded artery; [3] hemorrhagic infarction; [4] multi-territory ischemic lesions in both right and left anterior circulations or in both anterior and posterior circulation; [5] ischemic lesions in posterior circulation; and [6] cortical infarction.

In patients with CS, contrast saline transcranial color-coded sonography (TCCS) was carried out to investigate the presence of RLS (Fig. 1). TCCS was performed using an ultrasound unit (EUB-7500, Hitachi, Tokyo, Japan) with a 2.0-4.0 MHz sector transducer. The middle vertebral artery (MCA) and vertebral artery (VA) were identified, in accordance with previous reports (4). For all TCCS studies, the contrast studies were performed using 10 mL of agitated saline at rest and during the Valsalva maneuver. We classified the size of the PFO by TEE, as follows: small PFO (1-29 microbubbles); and large PFO ( $\geq 30$  microbubbles), using a modification of the criteria defined by Cabanes et al. (5). When patients had an RLS, they were assessed for DVT or PE by duplex ultrasonography and/or contrast-enhanced computed tomography (CECT). All duplex ultrasonography



**Figure 2.** Patient classification. In patients with cryptogenic stroke (CS), contrast saline transcranial color flow imaging was performed to investigate the presence of right-to-left shunt (RLS). When patients had RLS, assessments were performed to detect deep vein thrombosis (DVT) or pulmonary embolism (PE). CAE: cardioaortic embolism, LAA: large artery atherosclerosis, SAO: small artery occlusion

studies were performed by an expert sonographer (A.A.). P-DVT was defined as DVT in the popliteal, femoral, or iliac veins, and D-DVT was defined as DVT at all other locations. Patients were divided into three groups: CS with P-DVT and/or PE (P-DVT/PE) group; CS with D-DVT (D-DVT) group; and CS without DVT (no DVT) group. The clinical characteristics were then compared among the three groups.

The results were compared using the chi-squared test for the comparison of categorical variables and the Kruskal-Wallis test as a nonparametric analysis for comparisons among three groups. P values of  $<0.05$  were considered to indicate statistical significance. All statistical analyses were performed using the Statistical Package for Social Science (SPSS version 22) software package for Windows.

The Regional Ethics and Hospital Management Committee of Jikei University School of Medicine approved the

study from the Jikei Stroke Registry. The board waived the need for patient consent. The anonymous data that support the findings of this study are available from the corresponding author upon reasonable request.

## Results

### Clinical features of cryptogenic stroke with right-to-left shunt

One hundred ninety-four of the 906 ischemic stroke patients were diagnosed with CS. TCCS was performed for 187 patients, and 72 patients (37%) had positive RLS findings (Fig. 2). TEE was performed for 45 of 72 patients (63%), and it confirmed the diagnosis of RLS. Two patients refused to undergo a DVT examination. Four patients with D-DVT and one with P-DVT did not undergo CECT be-

**Table. Patient Characteristics.**

	P-DVT/PE (n=6)	D-DVT (n=15)	no DVT (n=49)	p value
Median of age, years (IQR)	78 (59-83)	76 (70-86)	65 (52-79)	<b>0.031</b>
Female, n (%)	4 (67)	9 (60)	12 (24)	<b>0.011</b>
NIHSS score, median (IQR)				
On admission	3.0 (1.0-11.5)	3.0 (1.0-16.0)	2.0 (0.5-4.5)	0.3
On discharge	3.5 (0.75-15.75)	0.0 (0.0-3.0)	1.0 (0.0-2.0)	0.095
Modified Rankin Scale, median (IQR)				
Before onset	2.0 (0.0-4.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	<b>0.027</b>
Three months after onset	2.0 (1.5-5.0)	1.0 (0.5-5.5)	1.0 (0.0-3.0)	0.205
Risk factor, n (%)				
Hypertension	4 (67)	11 (73)	35 (71)	0.954
Dyslipidemia	1 (17)	8 (53)	25 (51)	0.259
Diabetes mellitus	1 (17)	3 (20)	11 (24)	0.937
Family history of stroke	2 (33)	3 (20)	16 (33)	0.611
Smoker	2 (33)	2 (13)	15 (31)	0.394
Past history of stroke	1 (17)	3 (20)	11 (24)	0.937
Mean of D-dimer, mg/dL (SD)	13.8 (13.0)	8.71 (14.9)	1.59 (2.08)	<b>&lt;0.001</b>
DVT examination				
Venous ultrasound, n (%)	5 (83)	14 (93)	40 (82)	0.551
Time to venous ultrasound, median days (IQR)	3.0 (2.0-3.0)	2.0 (2.0-6.75)	3.0 (2.0-3.0)	0.944
Contrast enhanced CT, n (%)	5 (83)	11 (73)	30 (61)	0.438
Time to contrast enhanced CT, median days (IQR)	2.0 (2.0-3.0)	4.0 (2.5-4.0)	6.5 (5.0-9.0)	0.443
Time to first examination from stroke onset, median days (IQR)	2.5 (1.75-4.0)	2.5 (2.0-4.0)	4.0 (2.0-5.0)	0.289
Characteristic features of embolization, n (%)				
Sudden onset of symptom	1 (17)	3 (20)	11 (24)	0.937
Recanalization of occluded artery	0 (0)	3 (20)	9 (18)	0.502
Hemorrhagic infarction	2 (33)	5 (33)	9 (18)	0.393
Multi-territory ischemic lesions	<b>5 (83)</b>	<b>3 (20)</b>	<b>9 (18)</b>	<b>0.002</b>
Ischemic lesions in posterior circulations	1 (17)	7 (47)	20 (41)	0.379
Cortical ischemic lesions	6 (100)	11 (73)	34 (69)	0.281

CS: cryptogenic stroke, CT: computed tomography, D-DVT: distal deep vein thrombosis, IQR: interquartile range, P-DVT: proximal DVT, PE: pulmonary embolism, SD: standard deviation

\* p<0.001 vs. D-DVT group, p=0.002 vs. P-DVT/PE group

cause the use of contrast media was contraindicated or because consent could not be obtained. Nineteen patients without DVT on venous ultrasound did not undergo CECT. Of the CS patients, DVT or PE was detected in 21 patients (29%). D-DVT was detected in 19 patients (26%), P-DVT was detected in two patients (2.7%), and PE was detected in 5 patients (6.9%). The median time to first DVT examination from stroke onset was three days (interquartile range, 2.0 to 4.25 days).

The comparison of the baseline characteristics of the groups revealed that the D-DVT and P-DVT/PE groups had an older median age and included a larger proportion of females in comparison to the no DVT/PE group (p=0.031 and p=0.011, respectively, Table). In the P-DVT/PE group, the modified Rankin Scale score before stroke onset was higher in comparison to the other groups (p=0.027, Table). Additionally, the levels of D-dimer in the D-DVT and P-DVT/PE groups were higher than the level in the no DVT/PE group (p<0.001, Table). The time to first DVT examination from stroke onset and stroke risk factors did not differ to a statistically significant extent among the groups. In the P-DVT/PE group, five of the six patients (83%) had multi-territory

ischemic lesions, and this frequency was the highest among the three groups, and higher than that in the D-DVT group (p=0.002 and p=0.007, respectively, Fig. 3). Cortical ischemic lesions tended to be more common in the P-DVT/PE group than in the D-DVT and no DVT/PE groups; however, the difference was not statistically significant (p = 0.281). Two of the six patients in the P-DVT/PE group with multi-territory lesions had a small PFO confirmed by TEE. None of the patients who underwent TEE had findings that suggested pulmonary shunting, including microbubbles, through the pulmonary veins, and a delay before microbubbles appear in the left atrium after their first appearance in the right atrium (6). None of the patients who underwent CECT had findings that suggested pulmonary shunting.

### **A case report of cryptogenic stroke with DVT and PE**

A 75-year-old woman developed consciousness disturbance one day after undergoing total knee arthroplasty. A neurological examination showed right hemiparesis, with an NIHSS score of 16. Brain MRI revealed high-signal lesions in the bilateral cerebral cortex on axial diffusion weighted images (Fig. 4). An RLS was confirmed by TCCS. Addi-

tionally, duplex ultrasonography revealed DVT in the left soleus, posterior tibial and peroneal veins and CECT showed thrombus in the pulmonary artery at one day after the onset of symptoms. We carefully resumed anticoagulation therapy with unfractionated heparin. Carotid artery stenosis was not seen on cervical duplex ultrasound and cardioembolic sources of stroke were not detected by echocardiography or Holter ECG. Her symptoms gradually improved and her NIHSS score was 3 on discharge.

## Discussion

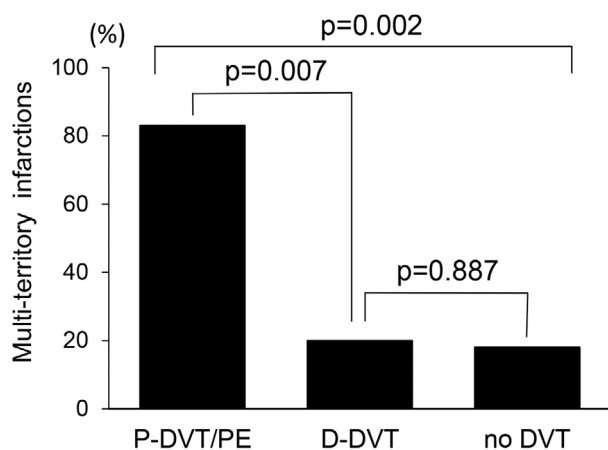
The present study demonstrated a number of findings. First, the P-DVT/PE group consisted of a large number of patients with multi-territory infarctions in both the right and left anterior circulations or in both the anterior and posterior circulation in comparison to the D-DVT group. Second,

29% of CS patients with an RLS had DVT. Third, the D-DVT and P-DVT/PE groups had a female predominance and the patients tended to be older, while the P-DVT/PE group tended to have pre-stroke disability.

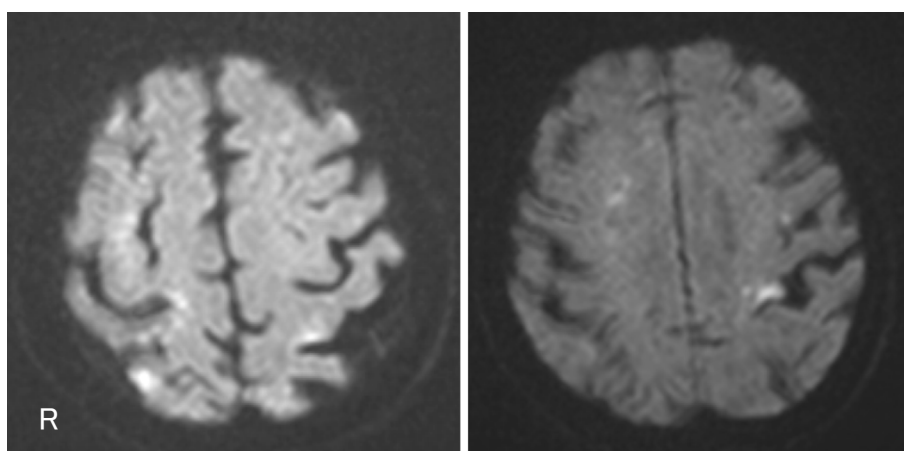
The present study showed that CS patients in the P-DVT/PE group more frequently had multi-territory infarction than those in the D-DVT group, since a large thrombus can contribute to the occurrence of embolic stroke (e.g., paradoxical embolism via an RLS) P-DVT/PE patients. With large thrombus, there may be a higher risk of recurrence of not only PE, but also paradoxical embolism in comparison to D-DVT. Thus, CS patients, especially those with multi-territory lesions, should immediately undergo CECT and venous ultrasound examinations, in order to initiate cautious observation and consider anticoagulation therapy according to the risk of bleeding complications.

In the present study, DVT was found in 29% of CS patients with an RLS. This is partially in concordance with previous research showing that 7-27% of CS patients with PFO had DVT (7-12). The prevalence of DVT in CS patients with an RLS has varied widely because the rates of antithrombotic usage and the methods and timing of DVT evaluation differed among the previous studies. The study by Liberman et al. (10) used the CCS system to define CS. In that study, only 7.6% of CS patients with PFO had DVT, and then the frequency of D-DVT was unknown. Because they did not perform CECT, the rate at which DVT was detected would have been lower in comparison to the present study. Early multi-modal examinations may contribute to the precise diagnosis of DVT in CS patients.

The present study is the first to demonstrate that female sex and old age are associated with a higher incidence of DVT and/or PE in CS patients with an RLS. Additionally, the modified Rankin Scale score before stroke onset tended to be high. In the general population, the incidence rates of DVT and PE increase exponentially with age (13), and they are somewhat higher in women during the childbearing



**Figure 3.** Prevalence of multi-territory infarctions in the three groups. In the P-DVT/PE group, five of the six patients (83%) had multi-territory ischemic lesions. This frequency was the highest among the three groups, and higher than that in the D-DVT group.



**Figure 4.** A case of cryptogenic stroke with deep venous thrombosis and pulmonary embolism. A 75-year-old woman developed consciousness disturbance one day after total knee arthroplasty. Head MRI revealed high-signal lesions in the bilateral cerebral cortex on the axial diffusion weighted images.

years, while after 45 years of age, the incidence is generally higher in men (13). The present result is not in line with the previous report that showed that limb weakness and stroke severity are major risk factors for DVT in acute stroke patients after admission (14). The reason for this may be that the DVT examination was performed immediately after stroke onset. In the present series, it is possible that most DVT developed before rather than after the onset of stroke. Because the clinical features of patients with DVT in the present study might be close to those of the general population (13), it appears that DVT in CS patients with an RLS is not an incidental complication after stroke, but the probable cause of paradoxical embolism.

The present study was associated with several limitations. First, the number of patients in the P-DVT/PE group was too small to permit an appropriate statistical analysis. The present observations require confirmation in a large study. Second, some of the patients did not undergo CECT; thus, the frequency of PE and pelvic vein DVT may have been underestimated. Since some of the patients in the D-DVT and no DVT groups did not undergo CECT, they might have been included in the P-DVT/PE group. However, these patients did not have any symptoms suggestive of PE (e.g., tachycardia, respiratory failure, or chest pain). Third, because TCCS was performed to identify RLS non-invasively, in some patients, the diagnosis of RLS was not ensured by TEE. However, the performance of TCCS in MCA monitoring is a highly sensitive method for detecting RLS (15), and the specificity and accuracy increased in subjects with both sufficient temporal bone and foramen magnum windows (16). Fourth, even though RLS was detected soon after the onset of stroke, the stroke in such patients does not always occur due to paradoxical embolism. Other stroke etiologies should be considered after the detection of RLS.

In conclusion, when CS patients with an RLS have PE or P-DVT, we should pay close attention to paradoxical embolism as a potential stroke mechanism. Even if PFO closure is widely accepted as the treatment for CS with an RLS, elderly patients will be excluded from consideration (17). Because the present study demonstrated that elderly patients tended to have DVT or PE, treatment strategies other than PFO closure should be considered. Thus, early evaluation to detect the presence of PE and the location of DVT would be useful to confirm that role of paradoxical embolism as a stroke mechanism and prevent stroke recurrence and PE by watchful management.

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

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