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Letter to the Editor

Chronic Lung Parenchymal Disease May Be Causally Associated With Cryptogenic Stroke With Massive Right-to-Left Shunt

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Dear Sir:

Paradoxical embolism through a right-to-left shunt (RLS) has been considered a possible cause of cryptogenic stroke. Intracardiac shunts, including patent foramen ovale (PFO), are the main source of RLS, and many studies have investigated the characteristics of PFO-related strokes.[1] Meanwhile, embolic strokes secondary to an extracardiac RLS are rare, and relatively few studies have described its association with stroke. The only focused source of extracardiac RLS is a pulmonary arteriovenous malformation (PAVM),[2] and the interpretation of patients with cryptogenic stroke with massive RLS in whom neither an intracardiac shunt nor PAVM can be identified is challenging. Herein, we aimed to explore the potential extracardiac factors contributing to cryptogenic strokes with massive RLS.

This retrospective observational study was approved by the Institutional Review Board of the Seoul National University Hospital (IRB No. 2109-036-1252), and the requirement of informed consent was waived. In a subset of patients with cryptogenic stroke enrolled in our stroke registry from January 2010 to November 2021, a transcranial Doppler (TCD) ultrasound bubble study was performed. Among them, we only included patients with massive RLS to minimize potential false positives in the TCD bubble study, wherein "massive RLS" was defined by the presence of "shower" or "curtain" appearance of microembolic signals.[3] Transesophageal echocardiography (TEE) was followed by the TCD bubble study in all included patients. Patients with coexisting potential stroke mechanisms, such as small vessel occlusion, large artery atherosclerosis, cardioembolism, and dissection, were excluded.

The clinical and radiological findings of the study population were obtained. The risk of paradoxical embolism (RoPE) score and Spencer grade at rest by TCD were measured. The patterns of magnetic resonance (MR) imaging, including diffusion-weighted imaging and MR angiography, were categorized according to the criteria of previous studies[4] with modifications. Among patients with massive RLS, additional diagnostic workups, including TEE and/or chest computed tomography (CT), were performed to identify the stroke etiology. Moreover, by reviewing contrast-enhanced chest CT and medical records, the presence of chronic lung parenchymal disease was investigated, including bronchiectasis, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, and lung cancer (Supplementary Methods).

In total, 49 patients with cryptogenic stroke having a massive RLS were analyzed to determine whether the RLS had a clear source (Figure 1). The detection rate of the RLS source using TEE and/or chest CT among the patients with massive RLS was 38/49 (77.6%), with 29 patients with PFO, 6 with atrial septal defect, and 3 with PAVM. The RLS source(+) and RLS source(-) groups showed similar patterns of vascular risk factors, RoPE scores, and stroke phenotypes (Table 1). The RLS patterns did not significantly differ between the two groups. Furthermore, there were no significant differences in the D-dimer levels or the presence of frequent atrial premature complexes or enlarged left atrium between the groups.

The composite of chronic lung parenchymal diseases was more prevalent in the RLS source(-) group than that in the RLS source(+) group (36.4% vs. 5.3%, P=0.018). Patients with chronic lung parenchymal diseases (bronchiectasis [n=1], COPD [n=2], and lung cancer [n=1]) in the RLS source(-) group tended to show even milder stroke severity and lesion burden than did those with PFO-related strokes (Table 2 and Supplementary Table 1).

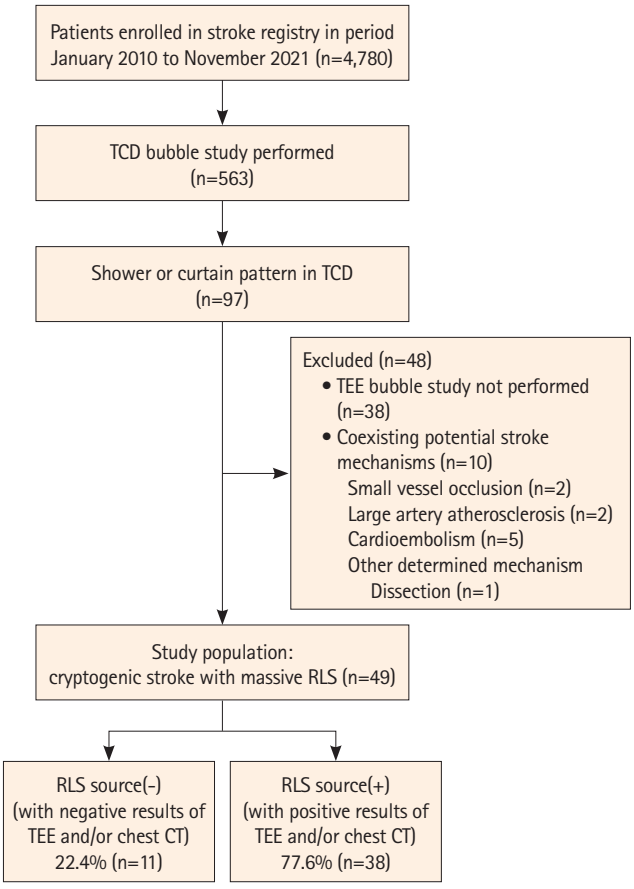

Figure 1. Flowchart of patient selection. TCD, transcranial Doppler; TEE, transesophageal echocardiography; RLS, right-to-left shunt; CT, computed tomography.

These findings suggest that chronic lung parenchymal disease may potentially contribute to cryptogenic strokes by causing a massive RLS through vascular remodeling. In such cases, the smaller shunt size associated with this mechanism may indicate a limited passage for large thrombi, which could explain the observed milder stroke phenotypes in our cases. Previous studies have clarified the vascular remodeling process in emphysematous lungs[5] and cancer.[6] Additionally, a few epidemiological studies have shown that 21%–26% of patients with COPD have intrapulmonary RLS,[7] and 55% with active cancer have RLS (intracardiac or intrapulmonary).[8] In situations where the conventional mechanisms of cancer-related stroke[9] may not adequately account for the findings, the presence of a massive RLS resulting from chronic lung parenchymal disease may be considered as an alternative mechanism. Further research is warranted to investigate this possibility in greater depth.

The diagnostic accuracy of TCD and TEE bubble studies should also be noted.[10] Despite the diagnostic values of TEE, many studies have shown that TCD bubble studies have better sensitivity for the detection of RLS,[3] probably due to the difficulties in TEE

Table 1. Comparison of RLS source(-) and RLS source(+) in cryptogenic stroke with massive RLS

	RLS source(-) (n=11)	RLS source(+) (n=38)	*P*
Age (yr)	64.7±10.3	61.3±13.9	0.459
Male sex	7 (63.6)	22 (57.9)	>0.999
Hypertension	6 (54.5)	16 (42.1)	0.510
Diabetes	3 (27.3)	4 (10.5)	0.178
Dyslipidemia	7 (63.6)	16 (42.1)	0.359
Smoking	4 (36.4)	13 (34.2)	>0.999
Obesity	1 (9.1)	9 (23.7)	0.419
Stroke history	2 (18.2)	5 (13.2)	0.646
NIHSS score			
Admission	4.5±7.3	2.0±3.0	0.291
Discharge	2.1±2.9	0.7±0.9	0.155
RoPE score	4.3±1.3	5.1±1.9	0.165
Lesion pattern			0.826
Single solitary lesion	4 (36.4)	14 (36.8)	
Single territory multiple lesions	2 (18.2)	6 (15.8)	
Multiple territory scattered lesions	1 (9.1)	8 (21.1)	
Large territory and additional lesions*	2 (18.2)	7 (18.4)	
TIA without lesion	2 (18.2)	3 (7.9)	
Vascular territory			0.646
Anterior circulation	5 (45.5)	22 (57.9)	
Posterior circulation	4 (36.4)	11 (28.9)	
Both	0 (0.0)	2 (5.3)	
TIA without lesion	2 (18.2)	3 (7.9)	
Angiographic finding			>0.999
No visible vessel occlusion	11 (100.0)	36 (94.7)	
Major artery occlusion	0 (0.0)	2 (5.3)	
Spencer grade at rest on TCD bubble study†			0.315
I	3 (27.3)	8 (21.1)	
II	3 (27.3)	3 (7.9)	
III	2 (18.2)	10 (26.3)	
IV	0 (0.0)	0 (0.0)	
V	3 (27.3)	17 (44.7)	
D-dimer (μg/mL; reference: 0.04–0.49)	0.3±0.2	0.8±1.2	0.080
Left atrial enlargement	2 (18.2)	13 (34.2)	0.464
Frequent atrial premature complex	0 (0.0)	2 (5.3)	>0.999
Chronic lung parenchymal disease	4 (36.4)	2 (5.3)	0.018

The results are presented as number (%) or mean±SD.
RLS, right-to-left shunt; NIHSS, National Institutes of Health Stroke Scale; RoPE, risk of paradoxical embolism; TIA, transient ischemic attack; TCD, transcranial Doppler; SD, standard deviation.
*At least one lesion size >15 mm; †Grade I (1–10 microbubbles), grade II (11–30 microbubbles), grade III (31–100 microbubbles), grade IV (101–300 microbubbles), and grade V (>300 microbubbles).

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Table 2. Stroke phenotypes of patients with chronic lung disease compared to PFO

	Chronic lung disease (n=4)	PFO (n=29)	*P*
NIHSS score			
Admission	0.5±0.6	2.3±3.4	0.012
Discharge	0.3±0.5	0.8±0.9	0.236
Lesion pattern			0.024
Single solitary lesion	0 (0.0)	8 (27.6)	
Single territory multiple lesions	2 (50.0)	4 (13.8)	
Multiple territory scattered lesions	0 (0.0)	7 (24.1)	
Large territory and/or additional lesions	0 (0.0)	7 (24.1)	
TIA without lesion	2 (50.0)	3 (10.3)	
Vascular territory			0.278
Anterior circulation	1 (25.0)	15 (51.7)	
Posterior circulation	1 (25.0)	9 (31.0)	
Both	0 (0.0)	2 (6.9)	
TIA without lesion	2 (50.0)	3 (10.3)	
Angiographic finding			>0.999
No visible vessel occlusion	4 (100.0)	27 (93.1)	
Major artery occlusion	0 (0.0)	2 (6.9)	

The results are presented as number (%) or mean±SD.
PFO, patent foramen ovale; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack; SD, standard deviation.

inspection. In our study, we specifically included only massive RLS cases confirmed via TCD bubble study. This was to highlight the unique subset of RLS sources demonstrating high shunt burdens but showing no PFO or PAVM on TEE and chest CT. However, the limited sensitivity of TEE in detecting extracardiac shunts, even in cases of massive RLS, might explain the low RLS source(-) detection rate. Conversely, unlike previous studies that suggested the extracardiac RLS pattern of higher bubble grade at rest compared with intracardiac RLS,[10] our study did not show any significant difference in RLS patterns between the RLS source(+) and source(-) groups. This trend might be partly due to the limited number of patients and the possibility of hidden PFO.

This study had several limitations. First, as a result of including only a small number of patients who met strict criteria at a single center, the statistical power was lowered. Longitudinal studies with larger populations are warranted to elucidate how lung parenchymal diseases contribute to RLS and subsequent strokes. Second, there may be a detection bias because chest CT is not routinely performed in patients with cryptogenic stroke (chest CT was performed in 8 out of 11 patients [72.7%] in the RLS source(-) group vs. 17 out of 38 patients [44.7%] in the RLS source(+) group). Third, there may be potential issues in merging both intra- and extracardiac shunts in the comparator group. However, considering the low prevalence of PAVM, it appears less likely that it would significantly distort the overall characteristics of the entire RLS source(+) group.

In conclusion, our findings suggest that chronic lung parenchymal disease may be a potential source of RLS in patients with cryptogenic stroke.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2023.01074.

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Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: JSK, KHJ. Study design: JSK, KHJ. Methodology: JSK, EJL, KHJ. Data collection: all authors. Investigation: all authors. Statistical analysis: JSK. Writing—original draft: JSK. Writing—review & editing: all authors. Funding acquisition: KHJ. Approval of final manuscript: all authors.

References

1. Mazzucco S, Li L, Binney L, Rothwell PM. Prevalence of patent foramen ovale in cryptogenic transient ischaemic attack and non-disabling stroke at older ages: a population-based study, systematic review, and meta-analysis. *Lancet Neurol* 2018;17:609-617.
2. Topiwala KK, Patel SD, Saver JL, Streib CD, Shovlin CL. Ischemic stroke and pulmonary arteriovenous malformations: a review. *Neurology* 2022;98:188-198.
3. Wessler BS, Kent DM, Thaler DE, Ruthazer R, Lutz JS, Serena J. The RoPE score and right-to-left shunt severity by transcranial Doppler in the CODICIA study. *Cerebrovasc Dis* 2015;40:52-58.
4. Bang OY, Seok JM, Kim SG, Hong JM, Kim HY, Lee J, et al. Ischemic stroke and cancer: stroke severely impacts cancer patients, while cancer increases the number of strokes. *J Clin Neurol* 2011;7:53-59.

5. Voelkel NF, Douglas IS, Nicolls M. Angiogenesis in chronic lung disease. *Chest* 2007;131:874-879.
6. Farnsworth RH, Lackmann M, Achen MG, Stacker SA. Vascular remodeling in cancer. *Oncogene* 2014;33:3496-3505.
7. Norris HC, Mangum TS, Kern JP, Elliott JE, Beasley KM, Goodman RD, et al. Intrapulmonary arteriovenous anastomoses in humans with chronic obstructive pulmonary disease: implications for cryptogenic stroke? *Exp Physiol* 2016;101:1128-1142.
8. Iguchi Y, Kimura K, Kobayashi K, Ueno Y, Inoue T. Ischaemic stroke with malignancy may often be caused by paradoxical embolism. *J Neurol Neurosurg Psychiatry* 2006;77:1336-1339.
9. Navi BB, Kasner SE, Elkind MSV, Cushman M, Bang OY, DeAngelis LM. Cancer and embolic stroke of undetermined source. *Stroke* 2021;52:1121-1130.
10. Mun JK, Park SJ, Kim SJ, Bang OY, Chung CS, Lee KH, et al. Characteristic lesion pattern and echocardiographic findings in extra-cardiac shunt-related stroke. *J Neurol Sci* 2016;369:176-180.

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Supplementary Methods

The clinical findings obtained in this study included demographic characteristics and vascular risk factors such as hypertension, diabetes, dyslipidemia, smoking, obesity, and previous history of stroke. Stroke severity was measured using the National Institutes of Health Stroke Scale by well-trained neurologists upon admission and discharge. The risk of paradoxical embolism score was calculated to evaluate the possibility of stroke associated with patent foramen ovale (PFO). The characteristics of magnetic resonance imaging performed within 7 days of the onset of symptoms were classified according to stroke lesion patterns, vascular territories, and angiographic findings. Stroke lesion patterns were categorized as single solitary, single territory multiple, multiple territory scattered, and large territory and/or additional. Vascular territories were categorized as anterior (anterior and middle cerebral arteries), posterior (vertebrobasilar artery), and both. Angiographic findings were categorized according to the presence of major arterial occlusions. Patients whose stroke lesions were not confirmed were classified separately as having a transient ischemic attack. D-dimer levels were assessed using a quantitative D-dimer latex agglutination assay. The size of the left atrium was measured using echocardiography, and measurements exceeding 40 mm were considered indicative of left atrial enlargement. Frequent atrial premature complexes were defined as cases where atrial premature complexes exceeded 1% of all heartbeats.

Additional tests performed within 2 weeks of the onset of symptoms to determine the etiology of cryptogenic stroke were as follows: transcranial Doppler (TCD) sonography bubble study, transesophageal echocardiography (TEE), and contrast-enhanced chest computed tomography (CT). The TCD bubble study was performed using a TCD monitoring device (PMD 150; Spencer Technologies, Redmond, WA, USA) and two 2-MHz probes fixed in a metal headframe (Marc 1500; Spencer Technologies). Microembolic signals (MESs) were detected by the monitoring device and probes heading toward the bilateral middle cerebral artery at depths of 40–60 mm through the temporal window. Agitated saline was prepared by mixing two syringes, one with 9 mL of 0.9% saline and the other with 1 mL of air connected by a three-way stopcock, which was injected three times through the antecubital vein. The procedure was performed during the Valsalva maneuver and at rest. MESs were recorded and counted using the computer software embedded in the device. All standardized protocols were performed by skilled sonographers. Right-to-left shunt (RLS) was classified as grade I (1–10 microbubbles), grade II (11–30 microbubbles), grade III (31–100 microbubbles), grade IV (101–300 microbubbles), and grade V (>300 microbubbles); including "shower" or "curtain" shunt patterns, defined as "massive RLS" in this study. In all patients with massive RLS in the TCD bubble study, the presence of PFO was confirmed with the TEE bubble study evaluated by cardiologists. Contrast-enhanced CT was considered when extracardiac RLS was suspected, as in pulmonary arteriovenous malformation (PAVM).

Chronic lung parenchymal disease was defined as a composite of bronchiectasis, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, and lung cancer. The diagnosis of chronic lung parenchymal disease before stroke was examined by reviewing medical records and tests, including chest CT and pulmonary function tests, and was deemed reliable only with official readings written by professional radiologists or pulmonologists or with biopsy confirmation. Lung cancer was defined as primary or metastatic lung cancer currently diagnosed, treated, or with a recurrence of prior inactive cancer within 6 months of stroke occurrence.

Statistical analysis

The study population was divided into RLS source(+) and RLS source(-) groups. The RLS source(+) group consisted of patients with a confirmed etiology of intracardiac RLS or PAVM. The remaining RLS source(-) group consisted of patients whose RLS source was not identified using the TEE bubble study and additional tests, including chest CT. To compare the data between the two groups, the Pearson χ^2 test or Fisher's exact test was used for nominal variables, and the two-sample t-test or Mann–Whitney U test was used for continuous variables. Subgroup analyses comparing the characteristics between the patients with chronic lung parenchymal disease in the RLS source(-) group and conventional PFO in the RLS source(+) group were also performed. These analyses were performed using R software for Windows version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

Supplementary Table 1. Representative cases showing massive RLS of undetermined source with chronic lung disease

	Patient 1	Patient 2	Patient 3	Patient 4
Sex	Female	Male	Male	Male
Age (yr)	65	68	80	78
Lesion pattern	Single territory multiple	TIA	Single territory multiple	TIA
Vascular territory	Left PCA	TIA	Left MCA	TIA
Major artery occlusion	None	None	None	None
Symptom	VFD	Left hemiparesis	Right hemiparesis	Right hemiparesis
NIHSS upon admission	1	1	0	0
NIHSS at discharge	1	0	0	0
Clinical recurrence	None	None	None	None
Stroke risk factor	HL	HTN, DM, HL, obesity	HTN, HL, smoking	HL, stroke history
RoPE score	6	3	3	3
Spencer grade at rest by TCD*	V	I	I	II
Microbubble detection by TEE	Faintly detected after more than 3 cardiac cycles	Absence	Absence	Absence
Chronic lung parenchymal disease	Bronchiectasis	COPD	COPD	HCC with lung metastasis
From lung disease detection to stroke	24 months	0 months (detected after diagnosis)	2 months	2 months
D-dimer (μg/mL; reference: 0.04–0.49)	0.16	NA	NA	NA

RLS, right-to-left shunt; TIA, transient ischemic attack; PCA, posterior cerebral artery; MCA, middle cerebral artery; VFD, visual field defect; NIHSS, National Institutes of Health Stroke Scale; HL, hyperlipidemia; HTN, hypertension; DM, diabetes mellitus; RoPE, risk of paradoxical embolism; TCD, transcranial Doppler; TEE, transesophageal echocardiography; COPD, chronic obstructive pulmonary disease; HCC, hepatocellular carcinoma; NA, not assessed.
*Grade I (1–10 microbubbles), grade II (11–30 microbubbles), grade III (31–100 microbubbles), grade IV (101–300 microbubbles), and grade V (>300 microbubbles).

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