Left-Sided Atrial Septal Pouch is a Risk Factor for Cryptogenic Stroke

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Background: The atrial septal pouch is an anatomic variant of the interatrial septum. The morphology of the left-sided septal pouch (LSSP) may favor blood stasis and predispose to thromboembolic events. The aim of this study was to determine the association between LSSP presence and cryptogenic stroke.

Methods: A total of 126 consecutive patients with cryptogenic stroke and 137 age-matched control patients without stroke were analyzed retrospectively. The presence and dimensions of LSSPs were assessed using transesophageal echocardiography.

Results: LSSP was present in 55.6% of patients with cryptogenic stroke and in 40.9% of those without stroke (P = .02). In univariate analysis, patients with LSSP were more likely to have cryptogenic stroke (odds ratio, 1.81; 95% CI, 1.11–2.95; P = .02). After adjusting for other risk factors using multiple logistic regression, the presence of an LSSP was found to be associated with an increased risk for cryptogenic stroke (odds ratio, 2.02; 95% CI, 1.19–3.41; P = .01). There were no statistically significant differences in size of the LSSP between patients with and those without stroke (P > .05).

Conclusions: There is an association between the presence of an LSSP and an increased risk for cryptogenic stroke. More attention should be paid to clinical evaluations of LSSPs. (J Am Soc Echocardiogr 2018;31:771-6.)

Keywords: Interatrial septum, Left atrium, Ischemic stroke, Cardioembolic stroke, Patent foramen ovale

Stroke is the fifth leading cause of death in the United States and a foremost cause of adult disability.[1,2] On average, someone in the United States has a stroke every 40 sec. Eighty-seven percent of these strokes are ischemic.[1] In approximately one third of ischemic strokes, the etiology is unknown despite a detailed workup; such strokes are classified as cryptogenic.[3] Cryptogenic strokes remain a diagnostic and therapeutic challenge. The primary difficulty in managing cryptogenic strokes is secondary stroke prevention, as the exact cause of the thromboembolic event remains unknown. Determining stroke etiology may significantly improve prognoses, medical therapies and the likelihood of reducing of stroke recurrence.

To reduce the incidence of cryptogenic stroke, researchers seek the possible sites of thrombus formation that may be the cause of thromboembolic events. An important role is assigned to the left atrium because it can be involved in a thromboembolic process via different mechanisms. Recently, the atrial septal pouch, which is a new anatomic entity within the interatrial septum, was described in an autopsy study performed by Krishnan and Salazar.[4] By definition, a septal pouch is a kangaroo pouch–like structure that occurs when the patent foramen ovale (PFO) channel is absent but the septum primum and septum secundum are partially fused.[5] The diverticulum may be located either on the right or left side of the interatrial septum.[4,5] Shortly after the septal pouch concept came to light, more than a dozen case reports noted that septal pouches located on the left side of the interatrial septum (left-sided septal pouches [LSSPs]) may be the site of thrombus formation and the source of ischemic strokes.[6-12]

Despite some evidence of LSSP involvement in the pathogenesis of cardioembolic stroke, the clinical significance of this mysterious structure remains unclear. The association between the LSSP and cryptogenic stroke on the basis of small preliminary epidemiologic retrospective studies is controversial.[13-18] Moreover, a recent meta-analysis by Strachinaru *et al.*[19] concluded that presence of LSSP does not correlate with an increased incidence of stroke, and further studies are necessary to validate its possible relationship with cryptogenic stroke. Thus, the main goal of our study was to

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Conflicts of Interest: None.

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Abbreviations

ICC = Intraclass correlation coefficient

LSSP = Left-sided septal pouch

PFO = Patent foramen ovale

RSSP = Right-sided septal pouch

TEE = Transesophageal echocardiography

determine if the presence of the LSSP may be a risk factor for cryptogenic stroke.

METHODS

The study was approved by the Bioethical Committee of Jagiellonian University in Cracow, Poland (122.6120.37.2016). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The methods were carried out in accordance with the approved guidelines.

Study Group

We retrospectively evaluated all Caucasian patients with cryptogenic stroke (first acute stroke) who underwent transesophageal echocardiography (TEE) from November 2008 to July 2017 in the 2nd Department of Cardiology at Jagiellonian University Medical College in Cracow, Poland ($n = 308$ patients). The modified TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria were applied to define cryptogenic stroke as an ischemic stroke in patients who had no definite source of cardioembolism, no large-artery atherosclerosis, and no small-artery disease and for whom the cause of stroke was not defined despite extensive evaluation.[20] All stroke cases were confirmed by magnetic resonance or computed tomography of the brain. We performed a chart review (history, physical examination, consultations, and outpatient notes) for all patients to collect demographic data and medical histories. A total of 308 consecutive patients with cryptogenic stroke were identified. Interatrial septal morphology was evaluated using TEE, and the recorded images were reevaluated by the authors. Patients with PFO channels, atrial septal defects, and atrial septal aneurysms were excluded from further analysis. In total, 126 patients with cryptogenic stroke were included in the analysis, and the prevalence of LSSP was determined in this population (Figure 1A).

Control Group

We identified 184 age-matched patients (Caucasian) without stroke who underwent TEE between February 2013 and July 2017 for any clinical reason other than stroke. Patients with histories of any type of stroke or transient ischemic attack were excluded from the study. Patients with PFO channels, atrial septal defects, and atrial septal aneurysms were excluded from further analysis. A total of 137 patients without stroke were included to serve as a control group (Figure 1B).

Two-Dimensional Transesophageal Echocardiographic Protocol

TEE was performed using a two-dimensional ultrasound system (Sonos 2000 [Philips Healthcare, Andover, MA] and Vivid E9 [GE Healthcare, Waukesha, WI]) with a 3.0- to 8.0-MHz transducer. The interatrial septum was assessed in midposition views of 90° to 120° (bicaval view) and in midposition views of 30° to 50° (short-axis view) during several cardiac cycles with color Doppler imaging in all patients.[21] The injection of agitated 0.9% saline solution (or 5% glucose solution) was performed at rest and during a Valsalva maneuver.

Image Interpretation

All transesophageal echocardiographic data sets were reviewed blindly and independently evaluated by two researchers. When two researchers (M.K.H., A.K.-O.) could not reach a consensus on interatrial septal classification in the same patient, the images were reevaluated by the third researcher (D.S.) until consensus was reached by the three investigators. First, screening for the PFO channel was performed, and this feature was detected when the channel was directly visible or when right-to-left shunting was demonstrated by color

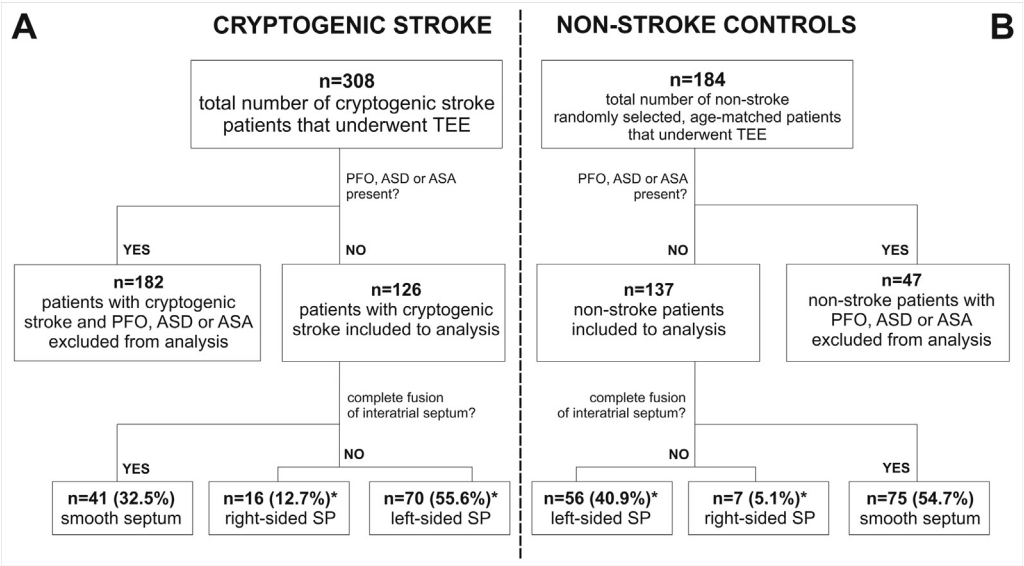

Figure 1 Flowchart outlining the study exclusion process. **(A)** Study group: patients with cryptogenic stroke (first acute stroke). **(B)** Control group (non-stroke). *ASA*, Atrial septal aneurysm; *ASD*, atrial septal defect; *SP*, septal pouch. *One patient had a double SP (coexistence of RSSP and LSSP in the same heart without the connection between both atria).

HIGHLIGHTS

- The authors demonstrate an association between the presence of LSSP and cryptogenic stroke.
- In patients with cryptogenic stroke, LSSP should be considered a possible site of thrombus formation.
- Large prospective trials are necessary to determine role of LSSP as an independent stroke risk factor.

Doppler during a Valsalva maneuver or microbubbles were seen in the left atrium after agitated saline injection and the Valsalva maneuver (Figure 2A). In addition, the presence of atrial septal defects and atrial septal aneurysms was evaluated using standard criteria.[22] The presence of a PFO channel, an atrial septal defect, or an atrial septal aneurysm was also confirmed by the original echocardiography report.

The interatrial septum was classified as an LSSP (Figure 2B), a right-sided septal pouch (RSSP; Figure 2C), or a smooth septum (Figure 2D). An LSSP was defined as a blindly ended diverticulum on the left side of the interatrial septum that is exclusively connected to the left atrium with no visible connection between the atria thorough the interatrial septum. An RSSP was identified in the same manner but on the right side of the septum.

The maximum depth and ostial height of the LSSP were measured in the bicaval 90° to 120° view, which anatomically corresponds to the long axis of the LSSP.[5] Transesophageal echocardiographic measurements were made in the 60% to 70% phase of the cardiac cycle (diastole). As described previously, we defined LSSP depth as the maximum distance from the pouch apex to its ostium. Ostial height was defined as the maximum distance between the LSSP free wall and the left atrial wall.[5] All linear measurements were collected using virtual calipers and were made by two independent researchers (M.K.H. and A.K.-O.) to reduce bias. The mean of the two measurements was calculated, with approximation to the 10th decimal place. Interobserver variability was calculated. Twenty randomly selected patients with LSSP were remeasured in a blinded fashion by the same observer 1 week after the original assessment to calculate intraobserver variability. LSSP volume was calculated using the following formula: volume (mL) = 0.013 × depth (mm) + 0.038 × height (mm).[5]

Statistical Analysis

Categorical results are presented as numbers and percentages. The Shapiro-Wilk test was performed to determine if the quantitative data were distributed normally. Quantitative results are presented as mean ± SD. Comparisons were performed using a *t* test or the Mann-Whitney test for two groups, depending on normality. Qualitative variables were compared using the χ^2 test of proportions for categorical variables. Multiple logistic regression analysis was performed to determine whether the effect of LSSP on cryptogenic stroke was modified by adjusting for age, sex, atrial fibrillation, congestive heart failure, coronary artery disease, arterial hypertension, dyslipidemia, smoking, and diabetes mellitus. The intraclass correlation coefficient (ICC) was used to assess inter- and intraobserver variability. An ICC > 0.8 indicated excellent agreement.[23] Statistical

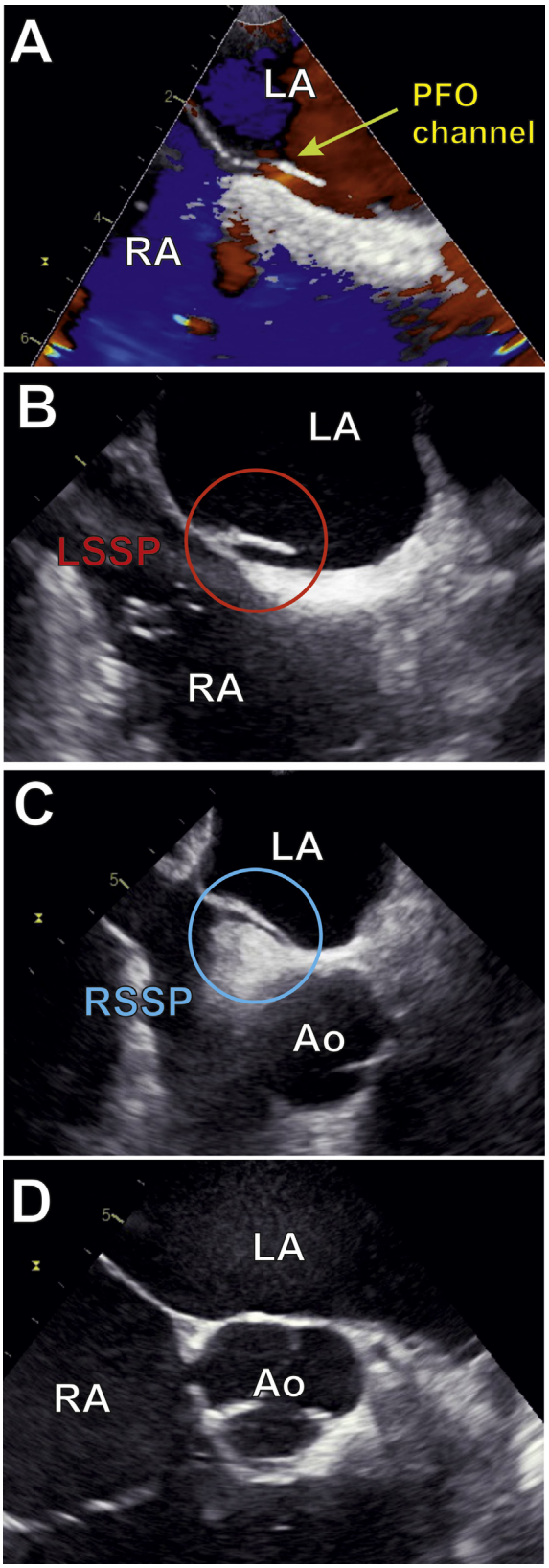

Figure 2 TEE of the PFO channel **(A)**, LSSP **(B)**, RSSP **(C)**, and smooth septum **(D)**. *Ao*, Aorta; *LA*, left atrium; *RA*, right atrium.

Table 1 Patient characteristics

Variable	Cryptogenic stroke (n = 126)	Nonstroke (n = 137)	P
Male/female	48.4%/51.6%	69.3%/30.7%	<.001*
Age (y)	43.1 ± 11.1	45.3 ± 10.0	.09
Body mass index (kg/m^2)	26.6 ± 4.1	25.7 ± 5.5	.14
Ejection fraction (%)	62.3 ± 7.7%	60.2 ± 14.3%	.15
Arterial hypertension	29.4%	42.3%	.03*
Atrial fibrillation	1.6%	16.1%	<.001*
Congestive heart failure	4.8%	10.2%	.10
Coronary artery disease	15.9%	16.1%	.96
Diabetes mellitus	9.5%	10.9%	.71
Ever smoker	19.8%	13.1%	.14
Hyperlipidemia	28.6%	36.5%	.17

Data are expressed as percentages or as mean ± SD.
*Statistically significant (χ^2 test).

analyses were conducted using STATISTICA version 13.1 (StatSoft, Tulsa, OK). A P value < .05 was considered to indicate statistical significance.

RESULTS

The mean age of the study group was 43.1 ± 11.1 years, and the mean age of the control group was 45.3 ± 10.0 years (P = .09). There were significantly more men in the nonstroke group compared with the cryptogenic stroke group (69.3% vs 48.4%, P < .001). Both atrial fibrillation and arterial hypertension were less common in the cryptogenic stroke group than in control subjects (P < .05). No other significant differences in patients' demographic data were found (Table 1). No thrombus or spontaneous echocardiographic contrast within the left atrium or left atrial appendage was found in all patients from both groups.

A lack of agreement in interatrial septal classification between two independent observers was noted in only 11 cases, and consensus was reached with a third researcher in all of these cases. An LSSP was present in 55.6% of patients with cryptogenic stroke and in 40.9% of those without stroke (P = .02). The prevalence of RSSP in these groups was 12.7% and 5.1%, respectively (P = .03). In univariate analysis, patients with LSSP were more likely to have cryptogenic stroke (odds ratio, 1.81; 95% CI, 1.11–2.95; P = .02). This finding was confirmed after adjusting for other stroke risk factors (age, sex, atrial fibrillation, congestive heart failure, coronary artery disease, arterial hypertension, dyslipidemia, smoking, and diabetes mellitus) via multiple logistic regression (odds ratio, 2.02; 95% CI, 1.19–3.41; P = .01). No thrombi were found within LSSPs.

The mean LSSP depth and the ostial height and volume in the patients with cryptogenic stroke were 8.4 ± 3.2 mm, 1.5 ± 0.8 mm, and 0.17 ± 0.06 mL, respectively. The mean dimensions of the LSSP in the nonstroke group were 9.5 ± 4.4 mm, 1.71 ± 0.84 mm, and 0.19 ± 0.08 mL, respectively. These values were slightly greater than those observed in patients with stroke, but no statistical significance was observed (P > .05). There were no differences in age between subjects with and without LSSP in the cryptogenic stroke and nonstroke groups or in the combined patient group (P > .05). The calculated intraobserver (LSSP depth: ICC = 0.95 [95% CI, 0.93–0.99]; LSSP ostial height: ICC = 0.91 [95% CI, 0.87–0.95]) and interobserver (LSSP depth: ICC = 0.83 [95% CI, 0.76–0.89]; LSSP ostial height: ICC = 0.85 [95% CI, 0.78–0.93]) variability showed excellent agreement for all sets of measurements.

DISCUSSION

Our study presents evidence of an association between the presence of an LSSP and cryptogenic stroke. The septal pouch is a relatively new discovery. Although the morphology of this feature is well recognized, its clinical significance is still not fully understood. The interatrial septum is incomplete during fetal life and physiologically fuses after birth. In approximately 25% of adults, a nonadherent flap valve of the septum and the rims of the fossa ovalis form a PFO channel.[2,4] The LSSP and RSSP arise as the result of PFO channel closure during postnatal life (partial fusion).[5] This process results in the presence of a blind pocket between the overlapping septal components, without a shunt between the atria.[4]

The LSSP is the most common anatomic variation of the human interatrial septum; its prevalence is nearly 50% in structurally normal autopsied human hearts.[4,24] The LSSP apex is always directed downward, with the ostium positioned toward the left and superior. The LSSP may resemble a calyx covered with endocardium and filled with blood.[5] All of these anatomic features predispose the LSSP to thrombus formation through the hemodynamic mechanism of local blood stasis. The second considered cause of thrombosis is chronic inflammation inside the pouch.[6] Furthermore, a possible protective mechanism against clot formation has been proposed. The hypothesis is that brisk laminar blood flow of the right pulmonary veins inhibits clot formation along the interatrial septum. When this protection is lost because of a condition such as high ventricular pressure, mitral stenosis, heart failure, or anomalies in pulmonary vein confluence, stasis may occur in the LSSP, with subsequent thrombosis.[6]

Our study found that the prevalence of RSSP was increased in the cryptogenic stroke group compared with patients without stroke (12.7% vs 5.1%, P = .03). The RSSP has no connection with the

left atrial cavity, and its presence does not affect the morphology of the left side of the interatrial septum. Therefore, in our opinion, the RSSP has no contribution to the pathophysiology of cryptogenic stroke. Moreover, a relatively small number of detected RSSPs may be the reason for this accidental statistical significance.

The present study is not without limitations. Our study was a retrospective, cross-sectional, single-center study, which may contribute to selection bias and have negative effects on the results. Nevertheless, we believe that the relatively large study group composed of consecutive patients accurately reflects the cryptogenic stroke population. We were unable to obtain left atrial volume and left atrial power in all patients; thus, they were not reported in this study. It is also possible that because of the nature of the patients with cryptogenic stroke, the interatrial septum in the stroke group was evaluated in much higher detail during TEE than the interatrial septum in the nonstroke group, in which patients were examined for other clinical indications, so the septum might not have been assessed in such detail. This may have introduced bias into our data by inadvertently increasing the prevalence of LSSP in the study group. However, we did not observe any differences in the quality of recordings, and at least two different transesophageal views of the interatrial septum were always available. Moreover, the assessment of patients was performed blindly.

The other main factor that may affect the results of this study is the age of the patients. It was proved that remodeling of the interatrial septum is a lifelong, continuous process in which the PFO channel evolves with age into a septal pouch or a smooth septum. The prevalence of the LSSP is highest among young adults (<50 years of age) and significantly lower in older subjects, among whom more cases with a smooth septum are observed.[5] Because the prevalence of an LSSP and the prevalence of cryptogenic ischemic stroke differ as a function of age, larger studies that include patients in all age groups will be very valuable. Furthermore, racial differences in the prevalence of LSSP have not yet been explored.

Because the presence of an LSSP was associated with an increased risk for cryptogenic stroke, especially in the multiple logistic regression model after adjusting for other stroke risk factors (two times higher), clinical evaluation of this feature can no longer be avoided. TEE appears to be the best technique for visualizing the LSSP, and this structure should be routinely evaluated during this examination.[19,21,25] The issue of whether all LSSPs or only pouches of a certain size and pouches under certain hemodynamic conditions should be recognized as a stroke risk factor must be investigated. In addition, a consensus should be established concerning whether the presence of an LSSP in cryptogenic stroke is an indication for introduction of anticoagulation in long-term treatment or other management. The methods for LSSP closure or pouch destruction may be developed and will more likely include transcatheter methods than surgical procedures. The use of radiofrequency thermal coaptation or a transcatheter suture to weld together the LSSP free wall and the left atrial tissue without leaving devices behind may be promising methods for closing this small structure.[26,27]

CONCLUSIONS

Our study demonstrated an association between the presence of an LSSP and cryptogenic stroke. Young adults may be particularly prone to stroke caused by the presence of an LSSP, and this structure should be routinely evaluated during TEE in such patients. Large prospective, multicenter trials are necessary to determine the precise role of the LSSP as an independent stroke risk factor.

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