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;■:■-■.)

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

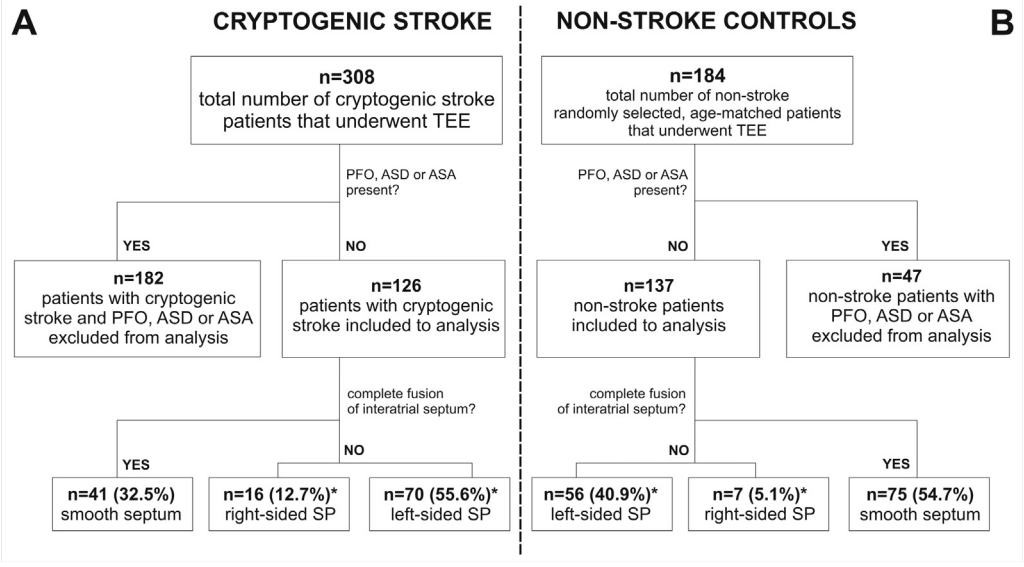

Figure 1 Flowchart outlining the study exclusion process. **(A)** Study group: patients with cryptogenic stroke (first acute stroke). **(B)** Control group (non-stroke). *ASA*, Atrial septal aneurysm; *ASD*, atrial septal defect; *SP*, septal pouch. *One patient had a double SP (coexistence of RSSP and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

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