Left-Sided Atrial Septal Pouch as a Risk Factor of Cryptogenic Stroke: A Systematic Review and Meta-Analysis

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Abstract

Background: Despite some evidence of left-sided septal pouch (LSSP) involvement in the pathogenesis of cardioembolic stroke, the question of LSSP clinical significance still remains unsolved. In this study, we aimed to determine the association between the LSSP presence and cryptogenic stroke using meta-analytical approach. Methods: We performed a systematic review of electronic databases for studies that compared the presence of LSSP in subjects with cryptogenic stroke and non-stroke control. Data were extracted and pooled into a meta-analysis. Results: Seven studies (400 cryptogenic stroke patients and 1,456 non-stroke controls) were included in the meta-analysis. A total of 138 LSSPs were identified among the cryptogenic stroke patients, with a pooled prevalence of 29.8% (95% CI 17.5–43.7%), and 268 LSSPs were identified in the non-stroke controls, with a pooled prevalence of 21.0% (95% CI 13.7–29.5%). After meta-analysis, the risk of cryptogenic stroke was higher in patients with an LSSP than in patients without LSSP (OR 1.52; 95% CI 1.15–2.00; p < 0.001). No significant heterogeneity was detected across the included studies (p > 0.05). Conclusion: Our meta-analysis demonstrated association between LSSP and cryptogenic stroke. In our univariate analysis, the risk of cryptogenic stroke is higher among patients with LSSP than in cases without the LSSP.

Introduction

Cryptogenic stroke is defined as a symptomatic cerebral infarction for which no probable cause is identified after standard workup. Cryptogenic stroke is diagnosed based on the exclusion of known causes of stroke [1]. Ischemic stroke that remains cryptogenic after a standard clinical evaluation accounts for 20–30% of all ischemic strokes and is more prevalent among young adults [2].

Both of the authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
Numerous mechanisms for cryptogenic stroke have been proposed [1, 3], including thrombosis inside the left-sided septal pouch (LSSP) [4, 5].

The concept of the atrial septal pouch emerged in 2010 and was defined as a small, kangaroo pouch–like structure located on the human interatrial septum [4]. A septal pouch develops postnatally as a result of the partial fusion of the patent foramen ovale (PFO) channel. A diverticulum that arises by this mechanism can be located on either the left or right side of the interatrial septum, and there is typically no connection through the pouch between the right and left atrium [5].

The LSSP was immediately linked to cardioembolic events and proposed as an important thrombogenic site for stroke, similar to the left atrial appendage, which was confirmed by many case reports [4, 6–8]. In subsequent years, several original studies focused on the role of the LSSP in stroke patients. Unfortunately, based on the preliminary epidemiologic retrospective studies, the association between the presence of LSSP and increased risk of cryptogenic stroke is controversial [9–15]. Therefore, here we aimed to determine whether LSSP is associated with cryptogenic stroke using a meta-analytical approach.

Methods

Search Strategy

We adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for systematic reviews and meta-analyses [16]. We conducted a systematic literature search of the PubMed, EMBASE, and Scopus databases. The terms “septal pouch” OR “atrial septal pouch” were used to search the electronic databases. The search was not restricted by language or time. The last literature search flagged entries on May 2nd, 2018. We subsequently reviewed and evaluated the reference lists of all eligible articles to ensure the identification of all relevant studies.

Eligibility Assessment and Data Extraction

We required that the studies (1) evaluated the interatrial septum morphology in humans, (2) reported the prevalence of LSSP in subjects with cryptogenic stroke, and (3) compared those patients with non-stroke control patients. Articles that were eligible for inclusion in the meta-analysis were assessed by all authors. We initially excluded the following types of papers: case reports, editorials, conference abstracts, and duplicate reports of the same study. All authors independently extracted data from the included studies. The extracted data included the year, country, study design, samples size, and characteristics of each group, as well as the number of LSSPs identified in each group. Moreover, we also identified data regarding the distribution of other stroke risk factors, such as atrial fibrillation, coronary artery disease, congestive heart failure, dyslipidemia/hyperlipidemia, diabetes mellitus, arterial hypertension, and history of smoking among cryptogenic stroke patients and non-stroke groups. In the event of data discrepancies, we contacted the authors of the original study, if possible, for further information. Any disagreements were addressed by obtaining a consensus.

Statistical Analysis

We performed a meta-analysis using the STATISTICA version 13.1 software (StatSoft Inc., Tulsa, OK, USA) with a Medical Bundle and MetaXL version 5.3 from EpiGear International Pty Ltd (Wilton, Queensland, Australia) to calculate the pooled prevalence of LSSPs. A p value less than 0.05 was considered to be statistically significant. Evidence of publication bias was investigated using a funnel plot and analyzed using the Egger method. We assessed heterogeneity among the included studies using the Cochrane Handbook’s Q test and I² statistics [17]. p < 0.05 or I² > 50% was considered to indicate significant heterogeneity. We applied the meta-analysis using a random-effects model. Qualitative variables were compared using the χ² test of proportions for categorical variables. Sensitivity analysis was performed by omitting one study at a time to evaluate the influence of a single study on the overall estimate.

Results

An overview of the study identification and selection process is summarized in Figure 1. We initially identified 55 unique records. Six additional publications were identified after a manual search. Forty-three records were excluded for being case reports, conference abstracts, editorials, reviews, book chapters, or dual publi-
LSSP and Cryptogenic Stroke

Discussion

Almost all morphological features of LSSP predispose to local blood stasis and thrombosis inside the pouch. The LSSP volume makes up only about 15% of the left atrial appendage volume. However, pouch orientation (the LSSP apex is always directed downward) might be more predisposed to thrombus formation [5]. Moreover, the LSSP was found to be associated with a 2-fold increased risk of atrial fibrillation [20]. Combination of these 2 factors might be a reasonable explanation for why the LSSP is associated with increased risk of cryptogenic stroke occurrence.

Our systematic review and meta-analysis show that cryptogenic stroke occurred 1.5-times more frequently in patients with an LSSP. A previous meta-analysis performed by Strachinaru et al. [27] focused on the presence of LSSP in patients with ischemic stroke as a whole group, as well as in a subset of patients with cryptogenic stroke. In their random-effects meta-analysis, Strachinaru et al. [27] detected no difference in LSSP prevalence between non-stroke controls and patients with ischemic stroke (HR 1.20; 95% CI 0.96–1.53; \( p = 0.14 \)). This was not surprising, as many other factors might be responsible for the occurrence of stroke, and the results of that meta-analysis were not adjusted for other stroke risk factors. Cryptogenic stroke was shown to appear more frequently in patients with LSSP (HR 1.53; 95% CI 1.07–2.24; \( p = 0.02 \)), but this was driven by only a single underpowered, small study performed by Wong et al. [11]. Therefore, consensus on the possible association between LSSP and cryptogenic stroke was not reached. The meta-analysis performed by Strachinaru et al. [27] did not include 3 studies that comprised current meta-analyses [12, 14, 15].

Sensitivity analysis showed that our meta-analysis is well balanced, and exclusion of only one study, which was the study conducted by Holda et al. [15], that also has the highest weight in our meta-analysis influenced the pooled estimates, shifting them to the lower border and on the verge of statistical significance (\( p = 0.051 \)). Exclusion of studies performed by Sun et al. [14] or Wong et al. [11] also shifted the results to lower values, but the overall model was still statistically significant (\( p < 0.05 \)). Exclusion of 3 studies such as by Tugcu et al. [9], Wayangankar et al. [10], and Strachinaru et al. [13] made the results of the meta-analysis more significant.

The limitations of this meta-analysis are caused by the disadvantages of each study included. Although the definition of cryptogenic stroke was similar in all in-
Table 1. Characteristics of studies included into meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Imaging method</th>
<th>Interatrial septum exclusion criteria</th>
<th>Cryptogenic stroke patients</th>
<th>Non-stroke control patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>Year</td>
<td>Country</td>
<td>Imaging method</td>
<td>Interatrial septum exclusion criteria</td>
<td>group characteristic</td>
<td>group characteristic</td>
</tr>
<tr>
<td>Tugcu et al. [9]</td>
<td>2010</td>
<td>USA</td>
<td>TEE</td>
<td>Presence of PFO, closed pouch, right-sided SP and ASD</td>
<td>69, 22, 47, 69.7±8.4</td>
<td>Consecutive patients with first acute ischemic stroke(^d)</td>
</tr>
<tr>
<td>Wayangankar et al.</td>
<td>2012</td>
<td>USA</td>
<td>TEE</td>
<td>Presence of PFO and ASD</td>
<td>66, 9*, 57*</td>
<td>Consecutive patients undergoing TEE</td>
</tr>
<tr>
<td>Wong et al. [11]</td>
<td>2015</td>
<td>USA</td>
<td>TEE</td>
<td>Presence of PFO and ASD</td>
<td>23, 7, 16</td>
<td>Consecutive patients undergoing TEE(^d)</td>
</tr>
<tr>
<td>Yilmaz et al. [12]</td>
<td>2016</td>
<td>Turkey</td>
<td>cMDCT</td>
<td>Presence of PFO, ASD and ASA</td>
<td>40, 13, 27, 42.0±6.7</td>
<td>18–55 years old patients with the acute stroke(^d)</td>
</tr>
<tr>
<td>Strachinaru et al.</td>
<td>2016</td>
<td>Belgium</td>
<td>TEE</td>
<td>–</td>
<td>45, 7, 38, 55.0±13.0</td>
<td>Consecutive patients admitted into the stroke unit undergoing TEE(^d)</td>
</tr>
<tr>
<td>Sun et al. [14]</td>
<td>2016</td>
<td>China</td>
<td>TEE</td>
<td>Presence of PFO and ASD</td>
<td>31(^e), 10, 21, 61.0±12.0 (total population)</td>
<td>Consecutive patients undergoing TEE(^d)</td>
</tr>
<tr>
<td>Hołda et al. [15]</td>
<td>2018</td>
<td>Poland</td>
<td>TEE</td>
<td>Presence of PFO, ASD and ASA</td>
<td>126, 70, 56, 43.1±11.1</td>
<td>Consecutive patients undergoing TEE with first acute ischemic stroke(^d)</td>
</tr>
</tbody>
</table>

* Calculated from the association between LSSP and cryptogenic ischemic stroke (OR 1.3; 95% CI 0.6–2.8) and other information extracted from the article.

\(^d\) Information that all stroke patients were cryptogenic was obtained after contact with the first author.

\(^d\) Modified TOAST criteria – no definite source of stroke despite a thorough diagnostic evaluation.

**TEE, transesophageal echocardiography; cMDCT, cardiac multidetector computed tomography; PFO, patent foramen ovale; SP, septal pouch; ASD, atrial septal defect; ASA, atrial septal aneurysms; n, number of patients; LSSP, left-sided septal pouch; NOMAS, Northern Manhattan Study.**
cluded studies (modified TOAST criteria), some discrepancies in the study group and control selection processes might affect the final results. One of the studies performed by Strachinaru et al. [13] did not exclude patients with the presence of a PFO and atrial septal defects. Such patients were excluded in the remaining studies because these structures have previously been associated with cryptogenic stroke (Table 1) [28]. Also, a significant number of patients were excluded from the included studies at baseline because the interatrial septum was not well-visualized or because saline contrast injection was not performed. All of the studies were retrospective cross-sectional studies; therefore, we were unable to determine whether having an LSSP increases cryptogenic stroke risk longitudinally. Additionally, the imaging method (transesophageal echocardiography and cardiac computed tomography) may have negatively affected the results due to inadequate visualization of the LSSP, which would have understated the prevalence of this feature in both groups. A study that compares different imaging methods for the LSSP is required to define the best imaging technique and projection [29]. Moreover, many cryptogenic stroke patients do not routinely undergo transesophageal echocardiography; as a result, all studies are subject to patients selection bias.

The main factor that might affect the results of the meta-analysis is the age of the patients. The remodeling of

![Forest plots of the prevalence of the LSSP in (a) cryptogenic stroke and (b) non-stroke control patients. LSSP, left-sided septal pouch.](image-url)
the interatrial septum is a continuous process in which the PFO channel evolves into a smooth septum or septal pouch. The prevalence of the LSSP is the highest among young adults and significantly lower in older patients, in which more cases with a smooth septum could be noticed [5, 9]. The mean age of the subjects included in each study group differed significantly between the non-stroke and cryptogenic stroke groups and between studies. Among the 7 studies included in the meta-analysis, only the studies performed by Yilmaz et al. [12], Wong et al. [11], and Hołda et al. [15] included young adult populations (Table 1). The cryptogenic stroke and non-stroke populations in the study performed by Tugcu et al. [9] were the oldest among all of the included studies, which may have influenced the results of this study and the original study’s conclusion that there is no significant association between LASP and cryptogenic stroke. In the study by Strachinaru et al. [13], the cryptogenic stroke group was significantly younger than the non-stroke controls (55.0 ± 13.0 vs. 65.0 ± 15.0-years-old; p < 0.0001), which may also have affected the results of this study, where in older patients the smooth septum might prevail over LSSP, and in younger patients the PFO might prevail over LSSP. As those studies by Tugcu et al. [9] and Strachinaru et al. [13] have a large weight (30%), the results of the meta-analysis might be affected, and the real association between LSSP and cryptogenic stroke in young adults may differ. However, our sensitivity analysis did not show that the exclusion of any of these studies makes analysis insignificant (online suppl. Fig. 1). No information about patient age was provided by Wayangankar et al. [10]. Since the ethnic differences in the LSSP prevalence are not recognized, they should be accounted for in further studies. Finally, the associations between LSSP and other types of cerebrovascular and systemic thromboembolic events should also be investigated.

**Conclusion**

In conclusion, our meta-analysis demonstrated an association between LSSP and cryptogenic stroke. In our univariate analysis, the risk of cryptogenic stroke was higher among patients with LSSP than in cases without the LSSP.

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**Disclosure Statement**

The authors declare no conflicts of interest in relation to the current work.
References


