REVIEW

The left atrial septal pouch as a risk factor for stroke: A systematic review

La poche septale atriale gauche comme facteur de risque embolique: une revue systématique

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Summary The left atrial septal pouch (LASP) is formed by incomplete fusion of the septum primum and septum secundum, leaving a cavity open towards the left atrium, but without interatrial shunting. There is no recommendation concerning strategy in the presence of a LASP, especially in the setting of stroke. The aim of this review was to determine whether the LASP could be incriminated as the aetiology of a stroke. We included all pertinent publications on the subject, and calculated hazard ratios for ischaemic stroke and cryptogenic stroke. There were only five case–control studies concerning the LASP, involving 516 stroke patients and 779 controls. Overall LASP prevalence was 21%, with a slightly higher prevalence in the cryptogenic stroke group (26%), but this difference was not statistically significant ($P=0.27$). In a random-effects meta-analysis, there was no difference between controls and patients with ischaemic stroke (hazard ratio 1.20, 95% confidence interval 0.96–1.53; $P=0.14$). Cryptogenic stroke appeared more frequently in patients with LASP (hazard ratio 1.53, 95% confidence interval 1.07–2.24; $P=0.02$), but this was driven by only one severely underpowered study. The published case reports demonstrated that thrombus formation inside the pouch can occur in the presence of major predisposing factors. The LASP can be a site for thrombus formation, leading to embolic events, but its presence does not correlate with an increased incidence of

Abbreviation: LASP, left atrial septal pouch.

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stroke. Associated factors should be taken into consideration in the setting of stroke. Further studies are necessary to validate a possible relationship with cryptogenic stroke.

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MOTS CLÉS
Poche septale atriale gauche ;
Accident vasculaire cérébral ischémique ;
Accident vasculaire cérébral cryptogénique ;
Thrombus intra atrial

Résumé La poche septale atriale gauche (LASP) est formée par une fusion incomplète du septum primum et du septum secundum. Il n’y a pas de recommandation concernant la conduite à tenir en présence d’un LASP dans le cadre d’une embolie. Le but de cette revue est de déterminer s’il est possible de l’incriminer comme étiologie d’un accident vasculaire cérébral ischémique (AIC). Nous avons inclus toutes les publications pertinentes sur le sujet et calculé les rapports de risque d’AIC et AIC cryptogénique. Il y a seulement cinq études cas-témoins concernant le LASP, totalisant une population de 516 patients d’AIC et 779 contrôles. La prévalence globale du LASP était de 21 %, avec une prévalence légèrement plus élevée dans le groupe AIC cryptogénique (26 %), mais cette différence était statistiquement non significative (P = 0,27). Selon notre méta-analyse il n’y avait pas de différence entre les témoins et les patients souffrant d’AIC (HR 1,20, IC 95 % 0,96–1,53 ; P = 0,14). Les AIC cryptogéniques semblaient plus fréquentes chez les patient ayant un LASP (HR 1,53, IC 95 % 1,07–2,24 ; P = 0,02), mais cette tendance est influencée par une seule étude de très faible puissance statistique. Les cas déjà publiés démontrent qu’un thrombus peut se former dans la poche en présence des facteurs prédisposants. Le LASP pourrait être un site favorisant la thrombogénèse, mais n’est pas associé à l’augmentation du risque d’AIC. Les facteurs associés doivent être pris en considération dans le contexte d’embolie artérielle. D’autres études sont nécessaires pour valider une possible relation avec les AIC cryptogéniques.

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Background

The fusion of the interatrial septum was initially thought to be homogenous all along the coaptation line. The absence of fusion of the completely developed septum primum and secundum defines the presence of a patent foramen ovale [1]. It was recognized surprisingly late that this fusion may just be incomplete, leading to the appearance of pouch-like structures on either side of the interatrial septum (Fig. 1). The left atrial septal pouch (LASP) was described in 2010 by Krishnan and Salazar [2]. From the beginning, there was concern regarding the potential for thrombogenesis inside this pouch [3]. It is possible that in certain conditions the LASP behaves like the left atrial appendage, presenting a risk for embolic events. Unlike the appendage, this pouch has no contractility of its own, being formed almost exclusively from fibrous structures [4]. Fortunately, its cranial opening is directly in the way of the flow coming from the right upper pulmonary vein (Fig. 1), which may facilitate a washing mechanism, preventing local stasis and clot formation [5].

Several reports have demonstrated the presence of thrombi in the LASP, mostly in the setting of factors that can be assimilated into the classical triad of Virchow: atrial fibrillation, left ventricular dysfunction and procoagulable state. Despite these findings, later in 2010, Tugcu et al. showed an absence of evidence for an association between stroke and the presence of LASP [6].

There is no clear recommendation regarding strategy in the presence of a LASP, especially in the setting of a cryptogenic stroke. The aim of this review was to determine whether we possess sufficient information to incriminate this anatomical structure as the aetiology of a stroke, or should simply discard it as an innocent bystander.

Methods

This systematic review was conducted in accordance with Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines [7]. We planned to include studies of the relationship between the LASP and stroke in adults. Studies were included if they reported at least one of the following: a relationship between a septal pouch and embolic events (stroke), a septal pouch and local thrombus formation or a septal pouch and cryptogenic stroke. We excluded studies only published as abstracts, reviews and duplicate reports of the same study.

We searched the following databases: PubMed (National Library of Medicine, National Center for Biotechnology Information); and EMBASE. The following search terms were used: "atrial pouch"; "septal pouch"; "atrial thrombus"; "septal thrombus"; and "septal pouch stroke". We also checked manually the reference lists of all relevant papers to identify any studies that might have been overlooked by the automated search. Only studies in English were considered. The last search was performed on 25 October 2016. The studies were screened independently by two investigators (M. S. and J. C.-R.), based on title and abstract. The

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full text of the relevant articles was then retrieved and matched against the inclusion and exclusion criteria. When no consensus could be reached, the senior investigators (T. V. and M.-D. G.) were consulted.

The primary analysis regarded the possible relationship between a LASP and stroke or cryptogenic stroke.

The risk of bias for each individual study was assessed using the Cochrane Collaboration’s tool [8]. We planned to assess publication bias by visual inspection of the funnel plot. Heterogeneity was tested by measuring $I^2$, as proposed by Higgins et al. [9]. When $I^2$ was <50%, significant heterogeneity was thought to exist. For high heterogeneity, a random-effects model was adopted. The results were displayed using Forest plots. Differences between proportions were estimated using the $\chi^2$ test. A two-tailed $P$ value of <0.05 was considered significant.

Results

The initial search identified 27 publications. The manual search revealed one supplementary publication. After title and abstract screening, nine publications were excluded, according to inclusion and exclusion criteria. There was no disagreement in the selection process. A total of five case–control studies [6,10–13] and 14 reports of LASP thrombosis [5,14–26] were included in the present review (Fig. 2).

Bias estimation

None of the studies was randomized. All studies reported blinded reading of the echocardiograms, but true blinding was unachievable because of the retrospective method. The outcome data were also gathered retrospectively, leading to a potential bias. Publication bias was impossible to estimate because of the low number of relevant studies (fewer than 10).

Case–control and population studies

The results of the five case–control studies are summarized in Table 1; they had a relatively limited number of patients. Two studies showed evidence of a higher prevalence of stroke in patients with LASP (Wong et al. [13] and Sun et al. [11]), while the others did not. The total population of the five case–control studies comprised 1361 subjects, with a total prevalence of LASP of 21% ($n=283$). Of 516 patients with stroke, 123 had a LASP (24%), and of 779 controls, 151 had a LASP (19%; $P=0.055$). When analysing the data available regarding 145 patients with cryptogenic stroke, 37 had

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Table 1  Case–control studies concerning the left atrial septal pouch.

<table>
<thead>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AS</td>
<td>CS</td>
<td>Control</td>
<td>AS</td>
<td>CS</td>
</tr>
<tr>
<td>Number of patients (n)</td>
<td>187</td>
<td>69</td>
<td>157</td>
<td>75</td>
<td>31</td>
</tr>
<tr>
<td>Age (years)</td>
<td>71</td>
<td>70</td>
<td>67</td>
<td>57 (total population)</td>
<td>70</td>
</tr>
<tr>
<td>LASP (n)</td>
<td>54</td>
<td>22</td>
<td>46</td>
<td>20</td>
<td>8</td>
</tr>
</tbody>
</table>

AS: all stroke; CS: cryptogenic stroke; LASP: left atrial septal pouch.
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Figure 2. Flowchart displaying the selection process for our study. LASP: left atrial septal pouch.

a LASP (26%), and of the 486 controls, 103 had a LASP (22%; \(P = 0.27\)).

The overall relationship of a LASP with ischaemic stroke (Fig. 3) displayed a hazard ratio of 1.2 (95% confidence interval 0.96–1.53; \(I^2 = 10\%\); \(P = 0.14\)), and with cryptogenic stroke (Fig. 4) displayed a hazard ratio of 1.5 (95% confidence interval 1.07–2.24; \(I^2 = 0\%\); \(P = 0.02\)).

Case reports

A careful internet search for reliable sources of information led to the discovery of only 14 reports describing 16 cases of thrombi or other masses in or originating from an atrial septal pouch thrombosis [5,14–26]. An overview of these reports is depicted in Table 2. We noticed that only one case proved to be a lipoma in the pouch [17]. In almost all cases there was at least one clear identifiable factor leading to thrombosis: atrial fibrillation/flutter (10 cases [63%]); left ventricular dysfunction (three cases [19%]); local stasis or endothelial lesion (one case with a giant pouch [18] and one case after heart transplantation [5]); or procoagulant state (one case). One case (6%) had no obvious cause of thrombosis, and resulted in repetitive stroke. In all other cases, anticoagulant treatment was indicated based on the clinical context (such as atrial fibrillation or mechanical heart valve), with good results. Six of the cases (38%) presented with embolic events probably related to the thrombus formation (four strokes and one coronary embolism for the LASP; one pulmonary embolism for the right atrial septal pouch).

Summarizing the available data

The first description [2] and the most recent pathological study [4] found a prevalence of around 40% of septal pouches opening towards the left atrium and 4% of pouches opening towards the right atrium.

The first case–control study was published in 2010 by Tugcu et al., who found that the prevalence of LASP was only 30%, and that no association could be established with ischaemic stroke in univariate or multivariable analyses [6].

In 2013, the largest study was published by Wayangankar et al., on 566 transoesophageal studies for all indications [12]. The overall prevalence of LASP was low (11%), and no statistical association was noted with cryptogenic stroke or with any other clinical or echocardiographic variable. No information was given, however, on the relationship with atrial fibrillation.

Three other case–control studies were published in 2015 and 2016. The designs were similar, relying on retrospective analysis of transoesophageal echographies performed on stroke patients or patients with other pathologies [10,11,13]. The study by Wong et al. demonstrated a significantly higher prevalence of LASP in the cryptogenic stroke group [13], but the stroke population was too small to be statistically strong in a multivariable analysis (75 stroke patients with 31 cryptogenic strokes). The study by Sun et al. showed that LASP is a significant risk factor for ischaemic stroke [11], also in a very limited stroke population (31 patients). The two studies with larger stroke populations (187 patients in Tugcu et al. [6]; 223 patients in Strachinaru et al. [10]) provided the same conclusion: no significant statistical association between LASP and stroke in general or cryptogenic stroke.

Numerical analysis of the pooled data seemed to indicate a tendency towards higher prevalence of LASP in the stroke group (24% vs. 19%; \(P = 0.055\)), but the \(P\) value remained non-significant. Our meta-analysis confirmed the lack of a statistically significant association between the two (Fig. 3). Concerning cryptogenic stroke, numerical data were non-significant (26% vs. 22%; \(P = 0.27\)), but the meta-analysis demonstrated that cryptogenic stroke occurred 1.5 times more frequently in patients with a LASP. By looking at Fig. 4, you can see that this trend is driven by a single study, which has the largest weight. However, when it comes to cryptogenic stroke population, this is precisely the study that is the most underpowered among those analyzed (only 31 patients). It is a well-known fact that by using the Mantel-Haenszel method, there is a danger of overestimating the weights. In such a situation, the weights cannot be interpreted as the amounts of information contributed by each study. However, studies with
small numbers of events are better analyzed using this method.

With respect to the most important question (i.e. is it dangerous or not to have a LASP?), the cases already described had a number of embolic events. However, thrombi were also found in situations where no stroke had occurred. In the majority of cases when a thrombus was present, a classical factor from the Virchow triad could be identified (blood stasis in atrial fibrillation or left ventricular dysfunction, procoagulable state or endothelial injury). Furthermore, treatment guidelines for the underlying pathology and for the respective factor were sufficient for a therapeutic decision, independent of the presence of the LASP, with a favourable clinical outcome (Table 2).

This ambiguity is sustained by our analysis, which was unable to find a statistical association between ischaemic stroke and LASP. The slight tendency towards a larger prevalence in the cryptogenic stroke group was statistically significant, but was driven by only one severely underpowered study.

The LASP is an anatomical variant of fusion of the inter-atrial septum, with an echography prevalence of around...
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Table 2  List of reports demonstrating a left atrial septal pouch mass.

<table>
<thead>
<tr>
<th>Case no. [Ref.]</th>
<th>LASP/RASP</th>
<th>Thrombus/mass</th>
<th>Context</th>
<th>Clinical scenario</th>
<th>Treatment and outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [20]</td>
<td>LASP</td>
<td>Thrombus</td>
<td>Atrial fibrillation</td>
<td>Asymptomatic, no stroke</td>
<td>Anticoagulant, disappearance of thrombus</td>
</tr>
<tr>
<td>2 [22]</td>
<td>LASP</td>
<td>Thrombus</td>
<td>Atrial fibrillation</td>
<td>Asymptomatic, no stroke</td>
<td>Anticoagulant, disappearance of thrombus</td>
</tr>
<tr>
<td>3 [14]</td>
<td>LASP</td>
<td>Thrombus</td>
<td>Atrial fibrillation</td>
<td>Chest pain, no stroke</td>
<td>Anticoagulant, unknown evolution</td>
</tr>
<tr>
<td>4 [26]</td>
<td>LASP</td>
<td>No</td>
<td>Negative</td>
<td>Cryptogenic stroke</td>
<td>Aspirin, with recurrent stroke</td>
</tr>
<tr>
<td>5 [24]</td>
<td>LASP</td>
<td>Thrombus</td>
<td>Atrial fibrillation</td>
<td>Heart surgery for aortic stenosis, no stroke</td>
<td>Anticoagulant, disappearance of thrombus</td>
</tr>
<tr>
<td>6 [17]</td>
<td>LASP</td>
<td>Mass (lipoma)</td>
<td>Atrial fibrillation, dilated cardiomyopathy</td>
<td>Asymptomatic, no stroke</td>
<td>Anticoagulant, no change</td>
</tr>
<tr>
<td>7 [23]</td>
<td>LASP</td>
<td>Thrombus</td>
<td>Atrial fibrillation</td>
<td>Asymptomatic, no stroke</td>
<td>Anticoagulant, disappearance of thrombus</td>
</tr>
<tr>
<td>8 [16]</td>
<td>LASP</td>
<td>Thrombus</td>
<td>Atrial fibrillation</td>
<td>Stroke, thrombus also in the LAA</td>
<td>Anticoagulant, disappearance of thrombus</td>
</tr>
<tr>
<td>9 [18]</td>
<td>LASP</td>
<td>Thrombus</td>
<td>No abnormal functional findings/local stasis</td>
<td>Recurrent stroke</td>
<td>Anticoagulant, disappearance of thrombus</td>
</tr>
<tr>
<td>10 [25]</td>
<td>RASP</td>
<td>Thrombus</td>
<td>Ancient deep venous thrombosis</td>
<td>Pulmonary embolism</td>
<td>Anticoagulant, reduction of the thrombus</td>
</tr>
<tr>
<td>11 [19]</td>
<td>LASP</td>
<td>Thrombus</td>
<td>Depressed LVEF</td>
<td>Surgery for severe aortic stenosis</td>
<td>Anticoagulant, disappearance of thrombus</td>
</tr>
<tr>
<td>13 [5]</td>
<td>LASP</td>
<td>Thrombus</td>
<td>Atrial flutter, depressed EF</td>
<td>Heart failure</td>
<td>Anticoagulant, disappearance of thrombus</td>
</tr>
<tr>
<td>14 [5]</td>
<td>LASP</td>
<td>Thrombus</td>
<td>Aortic stenosis, depressed LVEF</td>
<td>Heart failure</td>
<td>Surgery, anticoagulant, no recurrence</td>
</tr>
<tr>
<td>15 [21]</td>
<td>LASP</td>
<td>Thrombus</td>
<td>Atrial fibrillation</td>
<td>Stroke</td>
<td>Anticoagulant, disappearance of thrombus</td>
</tr>
<tr>
<td>16 [15]</td>
<td>LASP</td>
<td>Thrombus</td>
<td>Smoking and oral contraception</td>
<td>Coronary artery embolism</td>
<td>Anticoagulant, disappearance of thrombus</td>
</tr>
</tbody>
</table>

EF: ejection fraction; LAA: left atrial appendage; LASP: left atrial septal pouch; LVEF: left ventricular ejection fraction; RASP: right atrial septal pouch.

20% of the population [6,10–13]. The difference in prevalence can be explained firstly by methodology. The pathology studies rely on anatomical probing [2,4], thus probably overdiagnosing otherwise tightly shut cavities. The study by Tugcu et al. was designed to search for LASP by transoesophageal examination, while the others used routine examination protocols, not designed for the detection of the pouch, and probably leading to underdiagnosis of smaller pouches. An interesting hypothesis from Tugcu et al. is that, in hypertension, the increase in intra-atrial pressure might force shut an eventual LASP, accounting for the lower prevalence in hypertensive patients (also noted by Wong et al.). Countering this possibility is the fact that in most reported cases of thrombosis in the LASP (Table 2), where patients probably had elevated intra-atrial pressure, the left atrial wall of the pouch was rigid and uncompliant. It is thus theoretically possible that the thrombogenic potential of the LASP may also be related to the rigidity of its walls.

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Discussion

Practical and future considerations

The LASP is a normal variant of the interatrial septum, and the evidence presented so far cannot incriminate it as the aetiology of a stroke, in the absence of major predisposing factors for thrombosis that in themselves require treatment sufficient to prevent thrombosis recurrence.

The presence of a LASP should be noted during any transoesophageal echocardiography, but without any clinical implication. In the setting of stroke, especially without clear aetiology, this pouch should be thoroughly investigated, ideally with multiplane/tridimensional imaging, in order to exclude a thrombus. No clear consensus exists about whether the presence of a LASP alone in cryptogenic stroke is an indication for anticoagulation or other treatment (occlusion or surgical removal). In atrial fibrillation, when looking to exclude an intra-atrial thrombus, care should be taken to examine an existing LASP.

The difference between a LASP and a double interatrial septum with persistent interatrial cavity is sometimes difficult to distinguish [27]. In the latter case, the cavity is usually bigger, there is often a communication with the right atrium and the opening in the septum primum towards the left atrium is rather a fenestration in a membrane. The embryogenesis might be different, involving an accessory membrane, presumably a remnant of the superior part of the septum primum or a persistent left venous valve of the embryologic sinus venosus [28]. This structure has also been implicated in the appearance of embolic events [29,30]. We believe that a case presented in 2006 as a double interatrial septum was, in fact, a LASP (but not described as such at that time) [15].

Conclusions

The LASP can be a site for thrombus formation, leading to embolic events, but the presence of this anatomical feature is not correlated with an increased incidence of stroke. Associated factors should be taken into consideration in the setting of stroke. Further studies are necessary to validate a possible relationship with cryptogenic stroke.

Disclosure of interest

The authors declare that they have no competing interest.

References


Sources of funding

None.

Authors contribution

M. S. collected the data, did the statistical analysis and drafted the article. J. C.-R. collected the data and did the statistical analysis. T. V. and M.-D. G. handled supervision, reviewed the manuscript for key intellectual content and contributed to the writing of the manuscript.

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