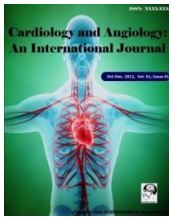

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Correlation of Left Atrial Septal Pouch with the Prevalence of Patent Foramen Ovale: A Retrospective Review

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Authors' contributions

This work was carried out in collaboration between all authors. Author ST designed the study, co-interpreted the studies and wrote the first draft of the manuscript. Author LHK managed the literature searches, analyses of the study and performed the final manuscript editing. Author SMR co-interpreted the studies and performed the initial manuscript editing and author SDT wrote the protocol and performed the initial manuscript editing. All authors read and approved the final manuscript.

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ABSTRACT

Purpose: To determine the prevalence of Left Atrial Septal Pouch (LASP) and assess the association with Patent Foramen Ovale (PFO).
Materials and Methods: We retrospectively reviewed 275 cardiac-gated CT examinations at Indiana University from January 2010 to June 2012, 160 cardiac CTs performed prior to pulmonary vein ablation, 115 for evaluation of coronary artery evaluation. Consensus readings were performed by two readers on a PACS workstation using the Multiplanar Reformat software to identify the presence or absence of LASP and PFO. PFO was diagnosed by the presence of a contrast jet extending from the left atrium to the right atrium.
Results: Overall prevalence of LASP was 24.7% (68 LASPs out of 275 patients). There was no

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significant difference regarding the gender and age between patients with and without LASP, p-values 0.054 and 0.63 respectively. The overall prevalence of PFO in both groups is low 2.2% (6 PFOs out of 275 patients). The prevalence of PFO in patients with LASP was 5.9% (4 out of 68 patients) and was 1.0% (2 PFOs out of 207 patients) in patients without LASP. There was a significant difference in prevalence of PFO between patients with and without LASP, p-value 0.035.
Conclusions: LASP is a common finding on cardiac CT, its prevalence not affected by age or gender. Patients with LASP have statistically greater prevalence of PFO than patients without LASP, but the prevalence remains low.

Keywords: Left atrial pouch; left atrium septal pouch; patent foramen ovale.

1. INTRODUCTION

Left atrial septal pouch (LASP) and patent foramen ovale (PFO) are both manifestations of interatrial septal developmental abnormalities. PFO is the sequelae of an unfused septum primum and septum secundum while LASP is the product of incomplete fusion, the residual unfused septum primum and septum secundum forming a flap in the left atrium. The prevalence of LASP was as high as 44.7% in the largest autopsy series [1] and its detectable prevalence on cardiac CT is between 11.5 to 40% [2,3]. The prevalence of PFO has been reported up to 25% of Transesophageal Echocardiography (TEE) [4] and between 22.6% and 23.5% on 64 Multidetector CT scan [2,5].

Our observation was that Atrial Fibrillation (AF) patients who underwent cardiac CT for pre-ablation mapping had high prevalence of LASP, a form of atrial septal abnormalities. Since PFO is also an atrial wall anomaly, we hypothesized that presence of LASP is associated with higher prevalence of PFO. Accordingly we sought to determine both the prevalence of LASP on cardiac CT and the strength of its association with CT detectable PFO.

To our knowledge, no publications in the literatures have investigated the co-existence of LASP and PFO.

2. MATERIALS AND METHODS

This retrospective study was approved by Institutional Review Board (IRB). The need for inform consent was waived.

A total of 275 cardiac CT examinations were performed. These included 160 pulmonary vein CT exams prior to pulmonary vein ablation and 115 coronary CTA exams for coronary artery evaluation. Studies were performed at Indiana University between January 2010 and June 2012.

2.1 CT Techniques

For CT of the pulmonary vein, a retrospective technique was applied with a Phillips 64 Brilliance (Philips Medical Systems, Cleveland, OH) multidetector CT scanner. We performed prospective or step and shoot technique on a Philips 256 iCT (Philips Medical Systems, Cleveland, OH) multidetector CT scanner based on rhythm, when possible, for pulmonary vein evaluation. No premedication was given. Intravenous contrast bolus tracking protocol was applied to optimize contrast enhancement in the left atrium. Images were reconstructed at 78% of the R-R interval. 3D images were created and stored on PACS for later evaluation. Multiplanar reformat software (MPR) was used for each study to better visualize the pulmonary vein ostium.

Coronary CTA protocol was tailored to each patient's cardiac history. In all cases, the target heart rate was less than 60 BPM. Retrospective, or prospective ECG gating techniques or occasionally a step and shoot technique by a Phillips 64 Brilliance or a Philips 256 iCT (Philips Medical Systems, Cleveland, OH) multidetector CT scanners were used with premedication by 5-25 mg intravenous Metoprolol for heart rate control and 2 tablets (0.4 mg) sublingual Nitroglycerin for coronary artery vasodilation (if not contraindicated). Cardiac-gated CT cathode tube modulation was used to reduce radiation exposure. The images were acquired 5-6 minutes after sublingual Nitroglycerin, if administered. Radiation technique, premedical-tion, and the amount and rate of contrast injection were under radiologists' supervision. Cardiac function calculation was post processed by radiologists at the Philips EBW workstations (Philips Medical Systems, Cleveland, OH).

For both groups, Isovue 370 was administered intravenously at the rate of 5 ml/s followed by saline flush. The amount of contrast was calculated based on the scan time, post threshold trigger delay, and location of tracker trigger region of interest in the ascending, descending aorta or left atrium. Image acquisition extended from the carina to the diaphragms.

The CT parameters were adjusted according to the patient's conditions (heart rate, age, BMI), clinical indications, available CT scanners (64 or 256 detector CT scanners), ECG gating technique and reconstruction techniques. We used 100-150 kV, 100-1050 mAs, 0.9 mm thickness with 0.45 increment and the fastest available rotation time (0.4s on 64 detector scanners and 0.27s on 256 detector scanners).

2.2 Image Analysis

Two radiologists reviewed the images retrospectively and reported the presence of PFO by consensus (ST, SMR). The studies were reviewed on a PACS workstation (Fuji Medical, Stamford, CT) using the MPR software. Radiologists were blinded to patient's clinical history any prior echocardiographic results.

Presence or absence of LASP and PFO was identified for individual patients. The imaging criteria of PFO, independent of the presence of LASP are based on the work from Kim et al [6]. We chose the most specific criteria for PFO, independence of a flow jet traversing the internal septum.

For atrial fibrillation patients, we measured LA size in the maximal transverse dimension on the axial plane.

2.3 Statistics

Demographic data and the presence or absence of both LASP and PFO on cardiac CTs were recorded. Statistical analysis was performed by Pearson Chi-Square test, ANOVA table and Fisher-Exact test depending on the quality and quantity of the variables. Presence of PFO, mean age and gender were analyzed by Fisher-Exact test, ANOVA table and Pearson Chi-Square test, respectively.

The difference in LA size between patients with and without LASPs was analyzed by student's t Test.

3. RESULTS

A total of 383 exams (203 Pulmonary Vein CT exams and 180 Coronary CTA exams) were performed between January 2010 and June 2012. One hundred and eight exams were excluded (43 exams from Pulmonary Vein CT and 65 exams from Coronary CTA) due to suboptimal diagnostic exams, known congenital heart disease, known prior pulmonary vein ablation, known coronary artery disease, prior coronary artery stent placement, or coronary artery bypass grafts.

A total of 275 exams (153 CT examinations of pulmonary veins and 122 CT Coronary angiogram) with adequate diagnostic quality were included, 68 patients with LASP and 207 patients without LASP, 118 female and 157 male. Patients with LASP had a mean age of 53.4±14 years (range of 22-82 years) and did not differ statistically from patients without LASP, mean age of 56.8 ±12.years (range 58-83 years), ($p > .05$). Neither did patients with and without LASP differ in gender, ($p > .05$).

The prevalence of LASP and PFO in atrial fibrillation patients were 24.8% and 1.9% respectively (39 LASPs and 3 PFOs out of 153 patients). Normal sinus rhythm patients showed similar trend. The prevalence of LASP and PFO were 23.8% and 2.5% respectively (29 LASPs and 3 PFOs out of 122 normal sinus rhythm patients).

Overall prevalence of LASP was 24.7% (68 out of 275 patients) and the prevalence was PFO was 2.2% (6 PFOs out of 275 patients). The prevalence of PFO in patients with LASP was 5.9% (4 PFOs out of 68 patients) and in patients without LASP was 1.0% (2 PFOs out of 207 patients) (Table 1).

There is significant difference in the prevalence of PFO between patients with and without LASP ($p<0.05$)

The size of LA in AF patients was not affected by presence of absence of LASPs. LA size in AF patients with and without LASPs was 4.3 cm (SD=0.9) and 4.2 cm (SD=0.8), respectively and did not differ significantly (p-value=0.37).

4. DISCUSSION

There are 2 possible theories for the existence of an LASP. The LASP may be the remnant of the embryologic left venous valve from the sinus venosus or, alternatively, it may be derived from an abnormal duplication or persistence septum primum or secundum [7]. Our hypothesis is that LASP and PFO are within the spectrum of developmental defects of the interatrial septum (Figs. 1-2). We propose that the LASP is the remnant of incompletely fused septum primum and septum secundum, while PFO is the sequel of unfused septum primum and septum secundum (Figs. 3-4).

Our study shows that the prevalence of LASP is high and that there is a significant association between LASP and PFO. The prevalence of PFO in the setting of LASP, however, remains relatively low, approximately 6%.

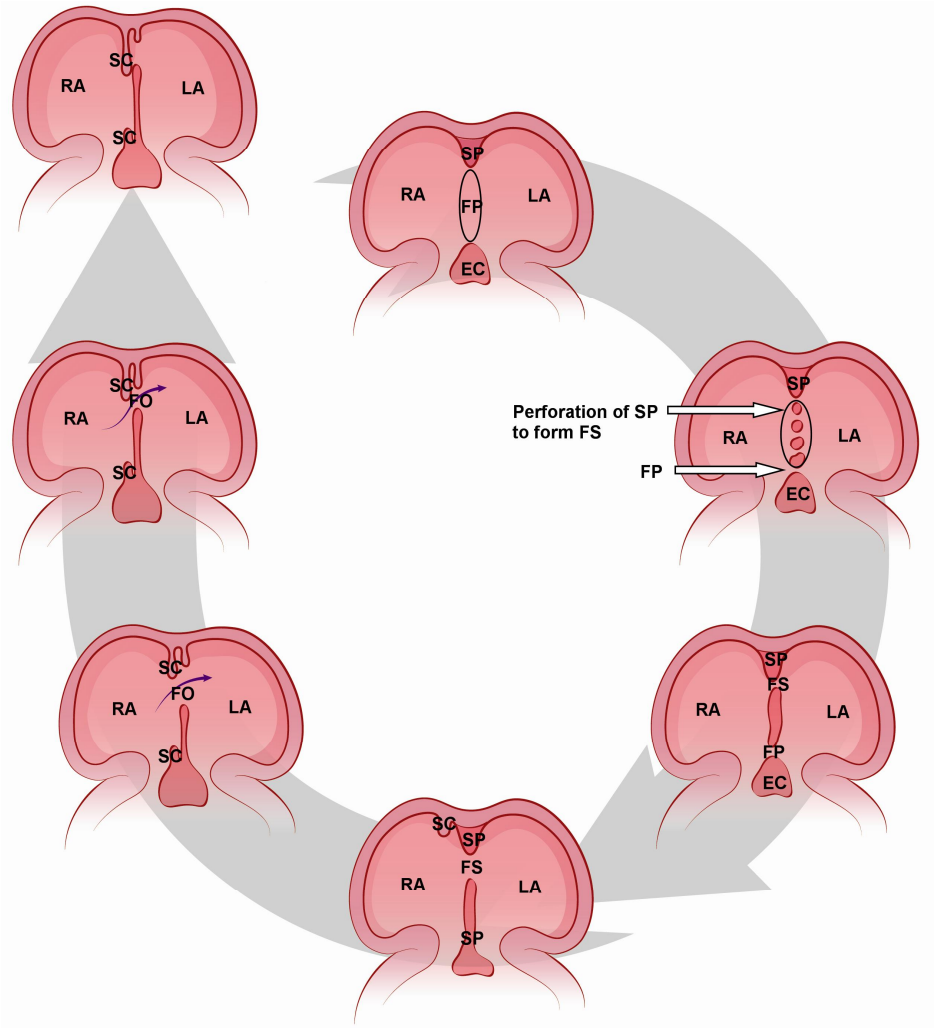


Fig. 1. The illustration shows the embryologic development of IAS in coronal plane. The septum primum is formed and expands, resulting in a smaller foramen; primum. The foramen secumdum is created by perforation of the septum primum followed by fusion of the small defects. At the same time, the endocardial cushion fuses with the septum primum becoming the lower part of IAS and upper part of IVS and creating separated atria. The septum secundum is formed and extended inferiorly to seal the foramen ovale. The 2 atria are finally completely separated by IAS. This illustration was modified from The Developing Human: Clinically Orientated Embryology, 8th edition, the cardiovascular System, page 299-300, copyright Elsevier (2008) with permission

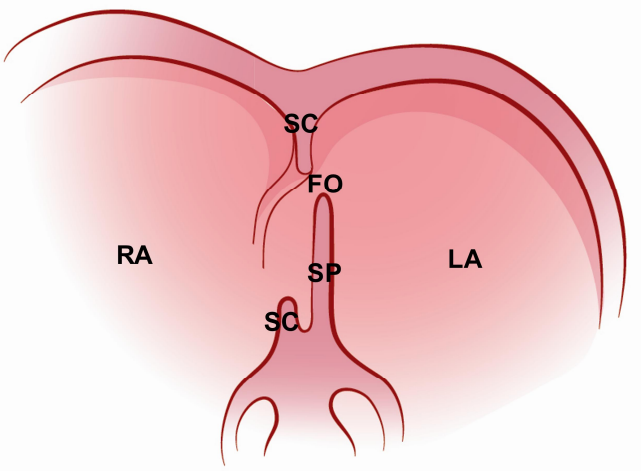


Fig. 2. The illustration shows the embryologic development of the Patent Foramen Ovale (PFO). If the septum secundum is not completely fused with the septum primum and persists as a flap against the foramen ovale, PFO, a persistent valve between RA and LA, occurs. This illustration was modified from The Developing Human: Clinically Orientated Embryology, 8th edition, the cardiovascular System, page 300, copyright Elsevier (2008) with permission

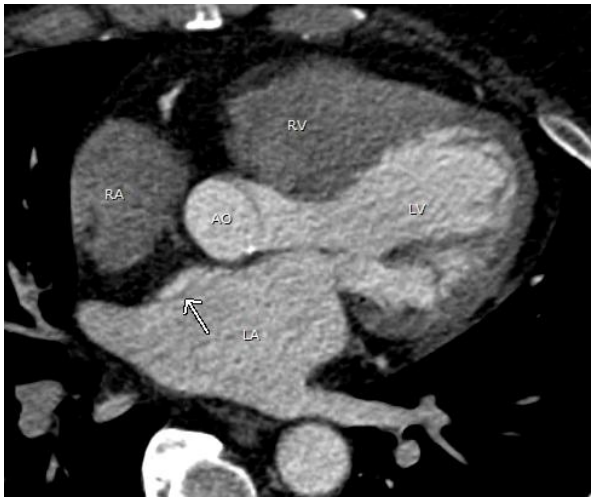
Table 1. A table demonstrated the results of statistical analysis of patients with LASP and without LASP with PFO, age and gender

	Present LASP N=68	Absent LASP N=207	p-value
PFO	4	2	0.035a
Gender	29	89	0.054b
Female			
Male	38	119	0.054b
Mean age (years)	53.41	56.75	0.063c
SD	14.48	12.19	0.063c

a: calculated by Fisher-Exact test , b: calculated by Pearson Chi-Square test, c: calculated by ANOVA test

We recognize that our study methods may have minimized the apparent association between PFO and LASP. The prevalence of these entities varies among studies and is dependent on the investigative approaches and patient population. Proposed CT criteria for the diagnosis of PFO have included visualization of the contrast jet from the left atrium to the right atrium, subjective recognition of LA enhancement before pulmonary vein enhancement, and software detection of early 1st peak of LA enhancement > of the maximal LA enhancement [3,5,8,9]. Williamson et al used 3 CT criteria to establish PFO: 1) presence of a distinct "flap" in the left atrium at the expected location of the septum primum (equivalent to an LASP), 2) a continuous column of contrast between septum primum and septum secundmum and 3) the presence of contrast jet into the right atrium [3]. Purvis et al reported 4.6% prevalence of PFO using the presence of a jet alone, and Kim et al found 2.1% on his series (2,6). Kim also demonstrated that presence of a jet alone was 98% specific and 73% sensitive for PFO (9) (Fig. 2). Our definition of PFO relied on this highly specific but only moderately sensitive finding, and accordingly we recognize that some PFOs that were present could have been missed. Accordingly we consider our observed co-occurrence of LASP and PFO to be a lower limit of the association.

Although Tugca et al. [10] did not find the association of LASP or Atrial Septal Pouch (ASP) or Double Atrial Septum or Left Atrial Roof pouch with ischemic or cryptogenic strokes, other investigators have suggested that LASP is a potential site of thrombus formation. Case reports have demonstrated LSAP as a potential cause of either cryptogenic stroke, other thromboembolic events such as a coronary embolus or a false positive diagnosis of atrial myxoma [11-17].



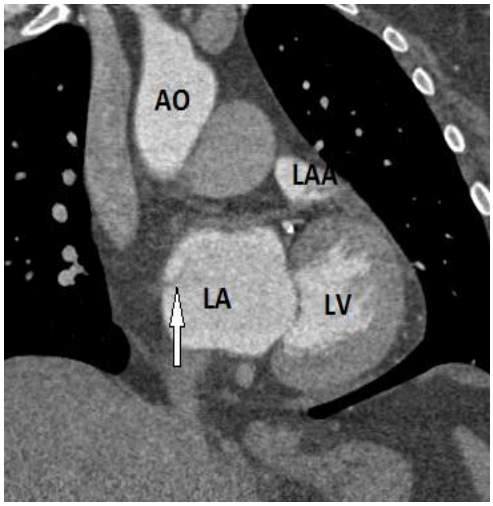
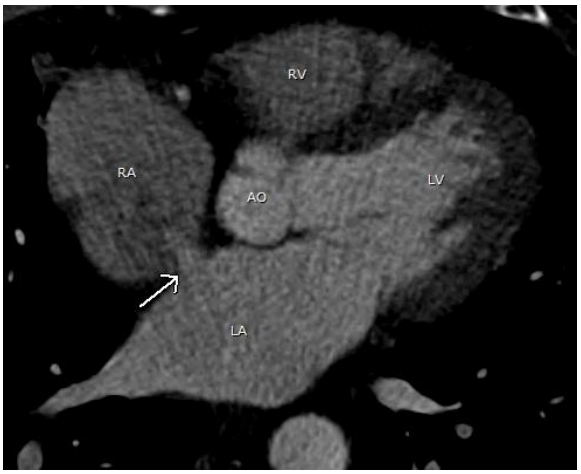


Fig. 3 A **Fig. 3B**

Fig. 3A-B: 59 year-old female with Atrial Fibrillation. Pre-ablation mapping for pulmonary ablation shows a slit-like structure in the right anterior left atrium on axial (arrow in Figure 3A) and coronal (arrow in Figure 3B), compatible with Left Atrial Septal Pouch (LASP). RA=Right Atrium, RV=Right Ventricle, LA=Left Atrium, LV=Left Ventricle and Ao=Aorta, LAA = Left Atrial Appendage



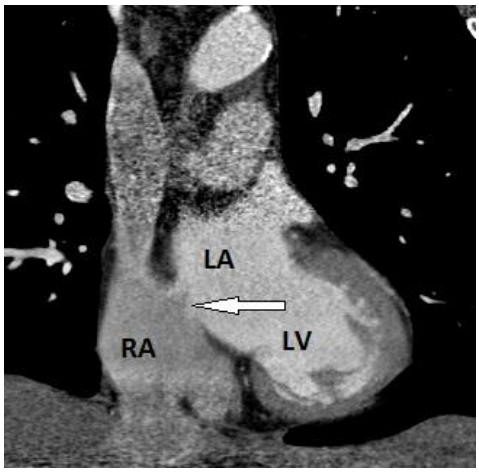


Fig. 4A **Fig. 4B**

Fig. 4A-B: 68 year-old female with Atrial Fibrillation. Pre-ablation mapping shows a jet of contrast from the left atrium to the right atrium via the small defect, suggestive of Patent Foramen Ovale (PFO) (arrows in Figure 4A and 4B). RA=Right Atrium, RV=Right Ventricle, LA=Left Atrium, LV=Left Ventricle and Ao=Aorta

The proposed etiology of stroke due to PFOs is different from that hypothesized for LASP, and is usually attributed to passage of paradoxical emboli during right to left shunting. Left to right shunting may predominate, with the pathogenic right to left shunt only being present episodically [18]. Regardless of mechanism, controversy also remains regarding the correlation of PFO and cryptogenic stroke. Some studies showed a positive correlation in young population (patients < 40 years old and a separate study of patients < 55 years old) [19,20]. At least one study has shown this correlation persists in older population (older than 55 years old) [20]. Some investigators

did not find this association [2], however there is consensus among investigators that presence of Atrial Septal Aneurysm (ASA) may increase the risk of stroke.

The clinical relevance of the co-occurrence of LASP and PFO remains to be determined. Answering this question would require a larger population based study in which both abnormalities are specifically evaluated by CT. In such a study additional co-variables that could independently increase the risk of embolic stroke via increasing left atrial stasis or augmenting right to left shunt would need to be included in the analysis. Assessment of left atrial size, atrial arrhythmias, evidence of elevated right heart pressures and possibly quantitation of PFO size could therefore be important.

Our study is limited by selection bias the lack of the gold standard for diagnosis such as TEE. In addition, our stringent definition of PFO resulted in a small number of positive cases of PFO, limiting the power of the study. Fortunately this limitation was not sufficient to confound our results.

5. CONCLUSION

LASPs are frequently detectable on cardiac CTA. PFOs are statistically more common among patients who demonstrate a LSAP but the prevalence remains relatively low. The potential significance of combined LASP and PFO on the incidence of embolic stroke is unknown and warrants further investigation.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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