

LEFT-SIDED ATRIAL SEPTAL POUCH AND RISK OF CRYPTOGENIC STROKE

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ABSTRACT

Introduction: Stroke is the second most cause of death worldwide after coronary artery disease. Left-sided atrial septal pouch (LASP) is associated with potential cardioembolic stroke. This study determines the association between LASP and cryptogenic stroke (CS) using cardiac multi-detector computed tomography (cMDCT) angiograms.

Materials and methods: This study included 40 patients with CS (23 males, mean age: 40.3 ± 10.4 years) and 40 age- and sex-matched healthy controls. cMDCT examinations by dual-source 64-slice MDCT with 0.6-mm slice thickness were performed for all patients and controls. The association between LASP and risk of CS was assessed after adjustment for other stroke risk factors.

Results: Patients with LASP were younger than control subjects (41.3 ± 7.2 years vs 44.2 ± 5.7 years; $p = 0.066$), with a comparable prevalence of hypertension (42.5% vs 35%; $p = 0.491$) and other risk factors. There were no differences in the prevalence of LASP between patients and controls (32.5% vs 25%; $p = 0.621$). LASP was observed in 43.5% ($n = 10$) of normotensive stroke patients compared to 15.4% ($n = 4$) of normotensive controls (Odds Ratio (OR): 4.23, 95% CI: 1.09-16.27, $p = 0.063$). On the other hand, LASP was detected in 17.6% ($n = 3$) of hypertensive CS patients compared to 42.9% ($n = 6$) of hypertensive controls (OR: 0.28, 95% CI: 0.05-4.23, $p = 0.253$). The presence of LASP was not associated with an increased risk of CS.

Conclusion: This study suggests that LASP is associated with CS. However, in normotensive individuals, LASP may be a minor risk factor for CS.

Key words: left-sided atrial septal pouch, cryptogenic stroke, multi-slice cardiac computed tomography angiogram.

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Introduction

Stroke is the second most cause of death worldwide after coronary artery disease⁽¹⁻⁴⁾. The incidence of stroke varies among countries and increases exponentially with age. Stroke is caused by an interruption of blood supply to the brain by a thrombus or bursting of an intracranial vessel. The imbalance between supply and demand in the territory of ischaemia causes infarction in the brain tis-

sue. In Western countries, approximately 80% of strokes are caused by focal cerebral ischaemia due to arterial occlusion, and the remaining 20% are caused by haemorrhages⁽⁵⁾. Acute ischaemic stroke (IS) was classified in the Trial of Org 10172 in Acute Stroke Treatment (TOAST) as large artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined aetiology and stroke of undetermined aetiology⁽⁶⁾. Embolism from the heart to the brain accounts for approximately

20% of all ischaemic strokes⁽⁷⁾. Patent foramen ovale (PFO) and atrial septal aneurysm (ASA) are the most common cardiac anomalies found in patients with stroke and transient ischaemic attack⁽⁸⁾. Concomitant ASA is the most likely potential cause of stroke risk in patients with cryptogenic stroke (CS) and PFO. Additional risk factors include the size of PFO, degree of shunting and coexisting hyper-coagulable state. Paradoxical embolism is believed to be a physiopathological mechanism, and deep lower extremity veins and superficial and pelvic veins are identified as sources of embolism. Recently defined as a new entity, left-sided atrial septal pouch (LASP) is associated with potential cardioembolic stroke⁽⁹⁻¹²⁾. LASP is caused due to an incomplete fusion of septum primum (SP) and septum secundum (SS), and it is a pouch that could be accessed from the left atrium. Based on these observations, we concluded that LASP might serve as a site for thrombus generation during a low-flow and/or hyper-coagulable states, similar to left atrial appendage, and might embolise to systemic circulation. Therefore, the aim of this study was to compare the prevalence of LASP between patients with CS aged <55 years and healthy subjects using cardiac multi-detector computed tomography (cMDCT) angiograms.

Material and methods

Study population

In total, 40 CS patients admitted to our neurologic intensive care unit who fulfilled the inclusion criteria of age between 18 and 55 years and the presence of suspected acute stroke were enrolled in this study during an 18-month period between 2010 and 2011. Written informed consent was obtained from each patient. The local ethics committee approved the study. The following routine diagnostic tests were performed for all patients: cranial computed tomography, magnetic resonance imaging of the brain, or both and duplex sonography of the extracranial and intracranial arteries. In patients with a suspected paroxysmal atrial fibrillation (PAF), 24-h Holter electrocardiography (ECG) monitoring was performed. All patients underwent transthoracic echocardiography (TTE) and ECG. Within a median of 3 days after stroke onset, all patients underwent transoesophageal echocardiography (TEE). TTE and TEE examinations were performed using Philips iE33 echocardiography system with 2.5- to 3.5-MHz transducer and 5-MHz

transducer, respectively, by the same cardiologist. Agitated saline was used as the contrast agent and injected while the patient was at rest and while a Valsalva manoeuvre was being performed. PFO and atrial septal defect (ASD) were diagnosed when the microbubbles were detected in the left atrium within three cycles after right atrium opacification. ASA was diagnosed when the excursion of abnormally redundant and mobile atrial septum was over 10 mm. After performing TEE, the cause of stroke was classified according to the TOAST criteria. Patients with stroke of cause that was unknown despite these extensive routine diagnostic examinations were diagnosed as having CS. A total of 40 age- and sex-matched healthy controls were selected among patients who had cMDCT angiogram performed recently, with no flow-limiting coronary artery lesions and no additional comorbidities. TTE was performed in the control group and no organic pathology was observed.

Cardiac multi-detector computed tomography (cMDCT) angiograms

All examinations were performed by a dual-source 64-slice multi-detector computed tomography (CT) (Definition, Siemens Medical Systems, Forchheim, Germany) by the same radiologist. Slice thickness was 0.6 mm, and temporal resolution was 83 ms. An iodinated contrast agent (350 mg/dL) was injected at a rate of 5 mL/s by a power injector. Retrospective ECG gating was performed, and images were reconstructed at 10% R-R intervals (from 10% to 100%). 4D care dose and ECG pulsing (30-80%) were applied to decrease radiation dose, and the mean estimated radiation dose was 7 millisieverts. All images were evaluated by four-dimensional INSPACE software on a Leonardo Workstation (Siemens Medical Systems, Forchheim, Germany) that allowed anatomical and functional evaluation of AS. Images were recorded and transferred to picture archiving and communications system. The CT criteria used for the detection of LASP were as follows: presence of a distinct flap or nidus in the left-sided septum and presence of a continuous column of contrast material between SP and SS without connection between the left atria and right atria.

Statistical analysis

The study results were analysed using Statistical Packages for Social Sciences (SPSS), version 17.00, for Windows software package

(Baskent University/Turkey, license code:7C6D064A B3 D2). Data are expressed as mean ± SD for continuous variables and as proportions for categorical variables. For continuous data, statistical differences were evaluated using Student’s t-test or Mann–Whitney U-test when the assumptions to use Student’s t-test were not satisfied. Chi-square test was used for comparison of qualitative data. All correlations were performed using Spearman’s rank correlation test. A p value of less than 0.05 was considered as statistically significant.

Results

The baseline characteristics of the study population are summarised in Table 1.

| Variables | CS patients (n=40) | Control subjects (n=40) | p value |
|------------------------------------|--------------------|-------------------------|---------|
| LASP | 13 (32.5) | 10 (25) | 0.621 |
| Age, years | 42.0±6.7 | 42.5±7.1 | 0.702 |
| Male | 20 (50) | 20 (50) | 1 |
| Body mass index, kg/m ² | 26.1±2.9 | 26.2±3.0 | 0.859 |
| Hypertension | 17 (42.5) | 14 (35) | 0.491 |
| Diabetes mellitus | 3 (7.5) | 4 (10) | 0.692 |
| Hypercholesterolemia | 12 (30) | 11 (27.5) | 0.805 |
| Smoking | 14 (35) | 17 (42.5) | 0.491 |

Table 1: Demographics and risk factors according to groups. Values are mean ± SD or n (%); LASP: left-sided atrial pouch, CS: cryptogenic stroke

There were no statistically significant differences in the baseline characteristics between the study groups. Patients with CS had a comparable prevalence of hypertension, smoking, dyslipidemia and obesity. cMDCT revealed LASP in 32.5% (n = 13) of patients with CS and in 25% (n = 10) of control group (odds ratio [OR]: 1.44, 95% confidence interval [CI]: 1.44-3.83, p = 0.621) (Table 2). LASP was observed in 43.5% (n = 10) of normotensive stroke patients compared to 15.4% (n = 4) of normotensive controls (OR: 4.23, 95% CI: 1.09-16.27, p = 0.063). On the other hand, LASP was detected in 17.6% (n = 3) of hypertensive stroke patients compared to 42.9% (n = 6) of hypertensive controls (OR: 0.28, 95% CI: 0.05–4.23, p = 0.253). The presence of LASP was not associated with increased risk of CS.

However, in normotensive individuals, LASP may be a minor risk factor for stroke.

| Variables | LASP (+) (n=13) | LASP (-) (n=27) | P value |
|---------------------------------------|-----------------|-----------------|---------|
| Age, years | 41.1±5.8 | 42.3±6.9 | 0.134 |
| Male | 5 (41.7) | 15 (53.6) | 0.49 |
| Body mass index, (kg/m ²) | 26.9±3.2 | 25.8±2.7 | 0.253 |
| Hypertension | 2 (16.7) | 15 (53.6) | 0.03 |
| Diabetes mellitus | 1 (7.1) | 2 (8.3) | 0.896 |
| Hypercholesterolemia | 4 (33.3) | 9 (32.1) | 0.941 |
| Smoking | 2 (16.7) | 12 (42.9) | 0.112 |

Table 2: Demographics and risk factors by LASP in CS patients. Values are mean ± SD or n (%); LASP, left-sided atrial pouch, CS (Cryptogenic stroke)

Conclusions

In the present study, we demonstrated that LASP was not more prevalent in patients with CS compared to age- and sex-matched healthy subjects, using cMDCT angiograms.

The closure of foramen ovale (FO) is an ongoing process throughout the lifetime. In utero, pressure gradient through the right atrium and left atrium forms a conduit, termed as FO, which provides shunting of oxygenated blood to the systemic circulation bypassing the lungs. After birth, the pulmonary vascular resistance increases via respiration and the pressure gradient fades about and the PFO closes physiologically. During the lifetime, adhesions between SP and SS serve an anatomical closure. This process occurs in about 75% of adults and fails to occur in the remaining 25%, which is termed as PFO (8,9). Recently, two investigators analysed the AS in an autopsy study and observed that 27% of specimens had PFO and only 28% of specimens showed a complete fusion of SS and SP.

The remainder (43%) had left-sided or right-sided atrial pouch^(9,10). The specimens with incomplete fusion of SP and SS were mostly from younger individuals. This observation raises the possibility that LASP serves as a nidus for thrombus formation and embolisation in low-flow and hyper-coagulable states.

Balli et al⁽¹³⁾, in their study using cMDCT images of the left atrium, suggested that LASP might serve as a nidus for thrombus formation and embolisation, which they verified using high-reso-

lution CT angiography images. On the other hand, Tugcu et al tested this hypothesis and the results did not support the association between the presence of an LASP and CS⁽¹⁴⁾. They assessed the presence of LASP by TEE in 187 patients aged >50 years (mean age: 70.6 ± 9.0 years) with first-ever ischaemic stroke and in 157 age-, sex- and race-matched control subjects. In this study, the prevalence of LASP was lower compared with the prevalence reported by Krishnan and Salazar⁽⁹⁾ and was not statistically significantly different between stroke patients and control subjects.

Furthermore, the study population was older and, similar to a PFO, the prevalence might decrease with advancing age. Krishnan and Salazar analysed a subgroup of patients with CS and postulated a similar prevalence of LASP⁽⁹⁾. They concluded that the presence of an LASP was not associated with ischaemic stroke in patients aged >50 years with first-ever IS and added that these results should not be generalised to patients aged <50 years with first-ever or recurrent ischaemic stroke and patients aged >50 years with a recurrent ischaemic stroke. However, they emphasised that LASP might be a contributing factor or might turn from an innocent bystander to a causative factor together with certain cofactors⁽⁹⁾.

In the present study, patients with CS had a similar prevalence of hypertension, obesity and smoking, which supports that additional risk factors for CS might contribute towards stroke in younger individuals. However, in normotensive individuals, LASP may be a minor risk factor for stroke. Increased after-load triggers left ventricular hypertrophy and later diastolic dysfunction and increased left atrial (LA) pressure. Consequently, increased LA pressure might force SP against SS and favour the fusion between the two septal components. The high frequency of hypertension and the consequent increased LA pressure might decrease the possibility of incomplete fusion of SP and SS and thus could be a possible causative factor. We found that hypertension was more prevalent in controls vs CS patients, similar to the above-mentioned hypothesis. We suggest that hypertension causes the fusion of SP and SS, thus decreasing the possibility of formation of a pouch for thrombus formation.

Conclusion

This study does not show any evidence of association between the presence of LASP and CS.

Furthermore, large prospective studies might reveal high-risk subgroups for CS in individuals with LASP.

Limitation of the study

The major limitation of our study is the relatively small sample size, which might have affected the statistical power to detect a significant risk associated with LASP.

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Author contributions

MY, MG, MK and TKY designed the study. MY, MSY and CK drafted the manuscript. All authors approved the final manuscript.

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