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Septal Pouch in the Left Atrium and Risk of Ischemic Stroke

Aylin Tugcu, MD,* Kazue Okajima, MD,* Zhezhen Jin, PHD,† Tatjana Rundek, MD,§ Shunichi Homma, MD,* Ralph L. Sacco, MD,§‖ Mitchell S. V. Elkind, MD,‡ Marco R. Di Tullio, MD*

New York, New York; and Miami, Florida

OBJECTIVES We sought to assess the association between the presence of a septal pouch in the left atrium and ischemic stroke.

BACKGROUND It has been suggested that the presence of a left septal pouch (LSP) may favor the stasis of blood and possibly result in thromboembolic complications. However, the embolic potential of an LSP is not known.

METHODS The association between an LSP and risk of stroke was assessed using a population-based case-control study design. The presence of an LSP was assessed by transesophageal echocardiography in 187 patients >50 years of age with a first-ever ischemic stroke (96 men, mean age 70.6 ± 9.0 years) and in 157 control subjects matched to patients by age, sex, and race/ethnicity. The association between an LSP and risk of stroke was assessed after adjustment for other stroke risk factors.

RESULTS Patients with LSPs were younger than control subjects (67.5 ± 9.1 years vs. 69.6 ± 8.8 years; $p = 0.046$), with a lower prevalence of hypertension (68.0% vs. 80.3%; $p = 0.01$). There were no differences in the prevalence of LSPs between stroke patients and control subjects (28.9% vs. 29.3%, respectively; $p = 0.93$). The subgroup of 69 patients (36.9%) with cryptogenic stroke showed a similar prevalence of LSPs (31.9% vs. 29.3%; $p = 0.70$). Multivariable analysis showed that the presence of an LSP was not associated with ischemic stroke (odds ratio: 1.09; 95% confidence interval: 0.64 to 1.85) or cryptogenic stroke (odds ratio: 1.41; 95% confidence interval: 0.71 to 2.78).

CONCLUSIONS This study does not demonstrate evidence of the association of the presence of an LSP with ischemic stroke or cryptogenic stroke. The stroke risk associated with LSPs requires further evaluation in the younger stroke populations. The cofactors that may turn an LSP from an innocent bystander to a causative mechanism for stroke remains to be elucidated. (J Am Coll Cardiol Img 2010; 3:1276–83) © 2010 by the American College of Cardiology Foundation

From the *Department of Medicine, Columbia University, New York, New York; †Department of Biostatistics, Columbia University, New York, New York; ‡Department of Neurology and Epidemiology, Columbia University, New York, New York; §Department of Neurology, University of Miami, Miami, Florida and the ‖Department of Epidemiology and Human Genetics, University of Miami, Miami, Florida. The study was supported by R01 NS36286 from the National Institute of Neurological Disorders and Stroke (NINDS). Dr. Di Tullio was the recipient of a NINDS Mid-Career Award in Patient-Oriented Research (K24 NS02241). All other authors have reported that they have no relationships to disclose.

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The causes of ischemic stroke remain unidentified by routine diagnostic testing in as many as 40% of patients (1). These strokes, often termed cryptogenic, have been linked to the presence of atrial septal abnormalities (2–6). The relationship between a patent foramen ovale (PFO) and cryptogenic stroke in younger stroke patients has been confirmed in multiple studies with transthoracic or transesophageal echocardiography (TEE) (4,7–9). The association has been more controversial in elderly subjects in whom it has been invoked or negated (4,10,11). Finally, a TEE study reaffirmed the relationship between a PFO and stroke risk in an older age group after adjustment for other stroke risk factors (12). The hypothesized stroke mechanism is paradoxical embolization or the embolization to the systemic arterial circulation of thrombus originating in the venous circulation. The presence of an atrial septal aneurysm (ASA) has also been associated with an increased risk of stroke, especially when it is associated with a PFO (13). In a meta-analysis, the stroke risk was higher in subjects with a PFO plus ASA than in those with either condition alone (11,14).

The diagnosis of cryptogenic stroke remains presumptive in a vast majority of patients and is based on the exclusion of other potential causes of cerebral embolism in the setting of an embolic-appearing stroke rather than on the actual demonstration of paradoxical embolization. Recently, a new anatomical entity, the left septal pouch (LSP), has been defined in a pathology study (15). An LSP was described as an incomplete fusion in the cranial segment of the overlap between the septum primum (SP) and septum secundum (SS), resulting in a recess that opens into the left atrium, with no interatrial shunting. It was hypothesized that, with access to the systemic circulation similar to that of the left atrial appendage, an LSP might serve as a nidus for thrombus formation in the presence of low flow states and therefore predispose to embolic events. An LSP has anecdotally been considered the culprit lesion for a transient ischemic attack and coronary embolus (16,17). An association between an LSP and stroke could provide novel insights into the mechanism of certain cryptogenic strokes. The aim of the present study was, therefore, to assess the existence of an association between an LSP and ischemic stroke.

METHODS

Study population. As part of the National Institute of Neurological Disorders and Stroke–funded Aortic Plaques and Risk of Ischemic Stroke study, 255 patients with acute ischemic stroke and 209 stroke-free control subjects were enrolled in the study between 1997 and 2002. The details of the study population were previously described (18). Briefly, stroke patients were consecutive patients residing in northern Manhattan and admitted to Columbia University Medical Center with a first acute ischemic stroke. All strokes were subtyped by a study neurologist on the basis of pre-defined criteria modeled after the Stroke Data Bank of the National Institute of Neurological Disorders and Stroke and TOAST (Trial of Organon in Acute Stroke Therapy) (19). Cryptogenic strokes typically had no definite source despite a thorough diagnostic evaluation. Control subjects were selected from the participants of NOMAS (Northern Manhattan Study) and matched to cases by age (within 5 years), sex, and race/ethnicity. Detailed recruitment methods for NOMAS were previously reported (20,21). Informed consent was obtained from cases and controls, or their health proxies when necessary. The study was approved by the Institutional Review Board of Columbia University Medical Center.

Definition of baseline subject characteristics. Cardiovascular risk factors were ascertained through direct examination and interview by trained research assistants. Hypertension was defined as a systolic blood pressure recording ≥140 mm Hg or a diastolic blood pressure recording ≥90 mm Hg based on the mean of 2 readings, a patient's self-report of a history of hypertension, or antihypertensive medication use. Diabetes mellitus was defined by a patient's self-report of such a history, insulin use, oral hypoglycemic use, or a fasting glucose ≥126 mg/dl. Hypercholesterolemia was defined as total serum cholesterol >240 mg/dl, a patient's self-report of hypercholesterolemia, or lipid-lowering treatment. Current smoking was defined by use of tobacco at the time of the interview; smoking history was defined by use of tobacco at any time. The presence of atrial fibrillation was documented based on the results of a current or past electrocardiogram. Coronary artery disease was defined as a history of myocardial infarction, coronary artery bypass grafting or percutaneous coronary intervention, typical angina, and use of antiischemic medications. Body mass index was calculated as weight (kilograms) divided by height (meters) squared. Race/ethnicity was de-

ABBREVIATIONS AND ACRONYMS

ASA = atrial septal aneurysm
CI = confidence interval
LSP = left septal pouch
OR = odds ratio
PFO = patent foramen ovale
TEE = transesophageal echocardiography

termined by subject's self-report using a questionnaire modeled after the U.S. Census Bureau questionnaire.

TEE evaluation. TEE was performed in stroke patients within 3 days of stroke onset and in control subjects on enrollment. A pre-defined protocol was used to assess for potential cardiac and aortic sources of embolism, including the assessment for the presence of a PFO at rest and during Valsalva maneuver using a multiplane transducer and agitated saline injection. After careful observation of the interatrial septum using 2-dimensional echocardiography and color Doppler mapping of the septum with the Valsalva maneuver, ≥2 intravenous contrast injections were administered through the right antecubital vein at rest and with the Valsalva maneuver. PFO was considered to be present if any microbubble was seen in the left atrium within 3 cardiac cycles from maximum right atrial opacification (2–4). An ASA was defined as more than a 10-mm protrusion beyond the plane of the septum into the left or right atrium (22). For the purpose of the present study, TEE was systematically reviewed for LSP presence. An LSP was defined as an incomplete fusion in the cranial segment of the overlap between the SP and SS in a standard bicaval view (Fig. 1A), with no evidence of right-to-left shunting on contrast injection at rest or during the Valsalva maneuver (Fig. 1B). The presence of a right septal pouch (incomplete septal fusion in the caudal segment of the septum with opening into the right atrium) or of a closed pouch (incomplete fusion of the septum without opening into either atrial chamber) was recorded. TEE studies were interpreted by 2 experienced echocardiography fellows (A.T., K.O.) blinded to subjects' case-control status, clinical characteristics, and stroke risk factors.

Interobserver variability. Twenty randomly chosen TEE studies were read by both observers independently for the presence or absence of an LSP. There was 100% agreement between the 2 observers (95% confidence interval [CI]: 86.7% to 100.0%).

Statistical analysis. Data are presented as mean ± SD for continuous variables and as proportions for categorical variables. Differences between proportions were assessed by the chi-square test and replaced by the Fisher exact test when the expected cell count was <5. Differences between mean values were assessed by the Student *t* test.

Univariable and multivariable logistic regression analysis was carried out to assess the association between an LSP (independent variable) and ischemic stroke (dependent variable). Variables significantly associated with ischemic stroke at univariable analysis (arterial hypertension, diabetes mellitus, hypercholesterolemia, smoking history, and atrial fibrillation) were entered as independent variables in the model, along with pertinent demographics (age, sex). The C statistic (equivalent to the area under the receiver-operator characteristic curve) was calculated to assess the performance of the logistic model.

SAS software (version 9.2, SAS Institute, Cary, North Carolina) was used in the analyses. A 2-tailed p value of <0.05 was considered significant for all analyses.

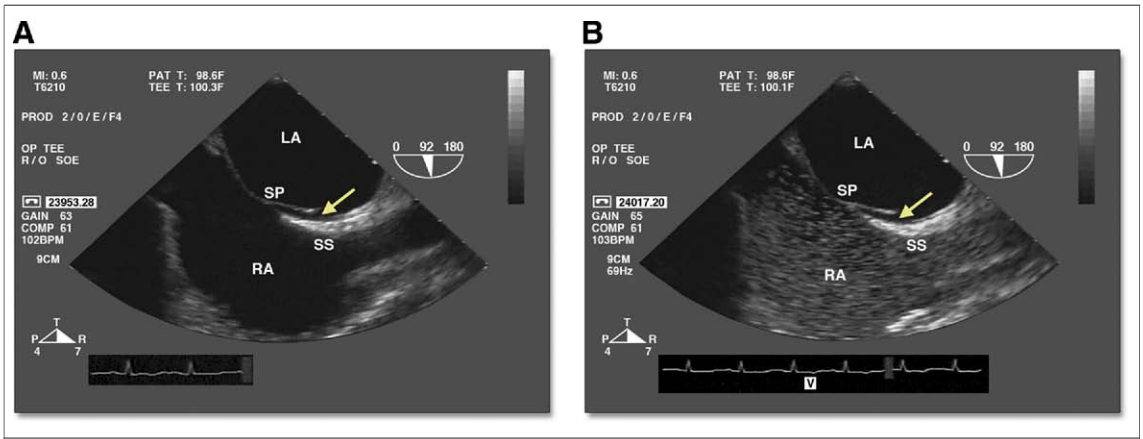

Figure 1. An Example of LSP Demonstrated by TEE

(A) Direct visualization of a left septal pouch (LSP) **(arrow)** by transesophageal echocardiography (TEE). In the longitudinal plane, an incomplete fusion is visible in the cranial segment of the zone of overlap between the septum primum (SP) and the septum secundum (SS). **(B)** Differentiation of an LSP from a patent foramen ovale by contrast TEE. Injection of agitated contrast saline with a Valsalva maneuver demonstrates the absence of microbubbles crossing the interatrial septum, excluding the presence of a patent foramen ovale. LA = left atrium; RA = right atrium.

RESULTS

Of the initial 464 subjects, 107 were excluded from the analysis because of the presence of a PFO (n = 89), a closed pouch (n = 9), a right septal pouch (n = 5), or an atrial septal defect (n = 4). Another 13 patients were excluded from the analyses because of a technically inadequate echocardiographic contrast study. The analyses were performed in the remaining 344 subjects.

Baseline characteristics. The final study population was composed of 187 stroke patients and 157 stroke-free subjects. The cause of stroke could be identified by means of routine diagnostic testing in 118 patients (63.1%). The stroke was classified as cryptogenic in the remaining 69 patients (36.9%). An LSP was detected in 100 subjects (29.1%); an ASA was found in 16 (4.7%).

Comparison of cases and controls. Demographics, cardiovascular risk factors, and atrial septal abnormalities in stroke patients and in control subjects are shown in Table 1. Stroke patients were significantly older than control subjects (70.6 ± 9.0 years vs. 67.0 ± 8.4 years; p = 0.0002) and had a significantly higher prevalence of hypertension and diabetes (both p < 0.0001). A history of atrial fibrillation was also more frequent in stroke patients than in control subjects (p = 0.02). The frequency of hypercholesterolemia was significantly lower in the stroke group (p = 0.045). There were no differences with regard to the prevalence of LSPs and ASAs in stroke patients compared with control subjects (28.9% vs. 29.3%; p = 0.93; and 5.9% vs. 3.2%; p = 0.24, respectively).

Comparison of patients with and without an LSP. Characteristics of subjects with and without an LSP are summarized in Table 2. Patients with LSPs were younger (67.5 ± 9.1 years vs. 69.6 ± 8.8 years; p = 0.046) and had a lower frequency of hypertension (68.0% vs. 80.3%; p = 0.01). The prevalence of ASAs did not differ between subjects with or without LSPs (4.0% vs. 5.0%; p = 0.71). Other demographic features and traditional risk factors were not significantly different between the 2 groups.

Association between an LSP and ischemic stroke. The subgroup of patients with cryptogenic stroke was compared with control subjects (Table 3). Cryptogenic stroke patients were on average 2 years older and had a higher prevalence of hypertension (79.7% vs. 66.9%; p = 0.05) and diabetes mellitus (37.7% vs. 22.9%; p = 0.02), and a lower prevalence of hypercholesterolemia (35.8% vs. 53.5%, p = 0.02). There was no difference with regard to the prevalence of LSPs and ASAs between the 2 groups.

The presence of an LSP was not found to be associated with an increased risk of ischemic stroke, either at univariable analysis (OR: 0.98; 95% CI: 0.61 to 1.56) or after adjustment for other stroke risk factors (OR: 1.09; 95% CI: 0.64 to 1.85) (Table 4). The presence of an LSP was also not found to be associated with an increased risk of cryptogenic stroke (Table 5).

DISCUSSION

This study does not demonstrate evidence of an association of the presence of an LSP with ischemic stroke. The lack of an association was also observed in a subgroup analysis of cryptogenic stroke cases in which the effect of new cardioembolic sources could be more relevant. Our results do not support the hypothesis that embolism from an LSP is a cause of ischemic stroke, even among patients without another apparent mechanism of cerebral ischemia.

The left atrium is a potential source of systemic embolization. Thrombus formation in the left atrium and its appendage in patients with atrial

Table 1. Demographics, Risk Factors, and LSP Frequency Status in Stroke and Control Subjects

	Stroke Patients (n = 187)	Control Subjects (n = 157)	p Value
Age, yrs	70.6 ± 9.0	67.0 ± 8.4	0.0002
<60	21 (11)	30 (19)	
60–69	69 (37)	70 (45)	0.009
≥70	97 (52)	57 (36)	
Male	96 (51.3)	88 (56.0)	0.38
Body mass index, kg/m^2	26.7 ± 5.1	27.6 ± 4.8	0.09
Race/ethnicity			
White	28 (15.0)	23 (14.7)	
Black	52 (27.8)	50 (31.9)	0.71
Hispanic	107 (57.2)	84 (53.5)	
Risk factors			
Hypertension	158 (85.0)	105 (66.9)	<0.0001
Diabetes mellitus	86 (46.5)	36 (22.9)	<0.0001
Hypercholesterolemia	78 (42.6)	84 (53.5)	0.045
Current smoker	33 (18.3)	25 (16.2)	0.61
Smoking history	103 (55.7)	99 (63.1)	0.17
Coronary artery disease	36 (19.4)	33 (21.0)	0.70
Atrial fibrillation	22 (11.8)	7 (4.5)	0.02
Atrial septal abnormalities			
ASA	11 (5.9)	5 (3.2)	0.24
LSP	54 (28.9)	46 (29.3)	0.93

Values are mean ± SD or n (%).
ASA = atrial septal aneurysm; LSP = left septal pouch.

Table 2. Demographics and Risk Factors by LSP Status

	LSP (+) (n = 100)	LSP (−) (n = 244)	p Value
Age, yrs	67.5 ± 9.1	69.6 ± 8.8	0.046
<60	22 (22)	29 (12)	
60–69	39 (39)	100 (41)	0.050
≥70	39 (39)	115 (47)	
Male	57 (57.0)	127 (52.0)	0.40
Body mass index, kg/m^2	27.0 ± 4.8	27.1 ± 5.1	0.88
Race/ethnicity			
White	10 (10.0)	41 (16.8)	
Black	28 (28.0)	74 (30.3)	0.18
Hispanic	62 (62.0)	129 (52.9)	
Risk factors			
Hypertension	68 (68.0)	195 (80.3)	0.01
Diabetes mellitus	42 (42.0)	80 (33.1)	0.12
Hypercholesterolemia	45 (45.0)	117 (48.8)	0.53
Current smoker	12 (12.5)	46 (19.3)	0.14
Smoking history	63 (63.6)	139 (57.2)	0.27
Coronary artery disease	15 (15.0)	54 (22.2)	0.13
Atrial fibrillation	10 (10.0)	19 (7.9)	0.52

Values are mean ± SD or n (%).
LSP = left septal pouch.

fibrillation and the consequent thromboembolic risk is well known (23–26). The pathogenesis of cryptogenic stroke in patients with interatrial septal abnormalities is not well understood. The morphologic characteristics of the interatrial septum that best predict the risk of thromboembolism remain unclear. It has long been debated whether the presence of a PFO actually plays a causal role in stroke or whether there is only a noncausal statistical relationship. Although there is considerable evidence that a PFO can cause ischemic stroke by means of paradoxical embolism, the difficulty of confirming the occurrence of embolism has led to the consideration of alternative explanations such as in situ thrombosis or atrial tachyarrhythmia (22,27). The former, however, is very rarely found by TEE or at autopsy. Although patients with interatrial abnormalities and stroke have lower thresholds for the induction of atrial fibrillation, this arrhythmia is rarely documented in patients with cryptogenic stroke and a PFO (27,28). Moreover, in patients with a cryptogenic stroke, approximately one third of discovered PFOs are likely to be incidental (29). Finally, the association between a PFO and stroke in the general population was not supported by 2 major studies (30,31). Therefore, there is an extensive ongoing search for other plausible mechanisms that may explain the origin of cryptogenic ischemic strokes.

An LSP was first described by Krishnan and Salazar (15) as a new anatomical entity with potential embolic complications. It was suggested that this pouchlike structure may favor the stagnation of blood, with consequent risk of thrombus formation and thromboembolic complications. In their study, the prevalence of an LSP was 39%, which is considerably higher than the prevalence of PFO in the general population (24%) (31). This observation might have great practical importance because evidence linking such a frequent entity to ischemic stroke could provide additional insights into the mechanisms of cryptogenic stroke.

After the exclusion of subjects with a PFO, an LSP was present in 29.1% of the subjects in our study, a prevalence that is lower compared with that in the previous study. Our patient population was considerably older (69 ± 9 years of age vs. 50 ± 21 years of age), and, similar to a PFO, the prevalence of an LSP might decrease with advancing age (32). In fact, subjects with an LSP tended to be significantly younger than subjects without an LSP, supporting this hypothesis. An LSP showed an equal distribution across sex, race-ethnic subgroups, and traditional risk factors analyzed, except for hypertension. Subjects without an LSP had a significantly higher prevalence of hypertension. One hypothesis regarding the lower frequency of LSPs in hypertensive subjects may be that an increased left atrial pressure might force the SP against the SS and favor the fusion between these 2 septal components.

We observed that the prevalence of LSPs was not significantly different between stroke patients and control subjects (28.9% vs. 29.3%). Given the often-discussed association of a PFO and cryptogenic stroke, we also undertook a subgroup analysis for patients with cryptogenic stroke, which also showed that the prevalence of LSPs did not differ between cryptogenic stroke patients and control subjects (32.4% vs. 29.8%). Both univariable and multivariable analyses revealed that an LSP did not have any impact on either ischemic (adjusted OR: 1.09; 95% CI: 0.64 to 1.85) or cryptogenic (adjusted OR: 1.41; 95% CI: 0.71 to 2.78) stroke. These findings suggest that an LSP is more likely an innocent bystander than a potential thrombogenic source. However, our results may not exclude the possibility that in the presence of associated cofactors, such as hypercoagulability, an LSP may favor thrombus formation and therefore cerebral embolization.

Study limitations. This case-control study is the first to date that assessed the role of an LSP as a stroke

Table 3. Demographics, Risk Factors, and LSP Frequency in Cryptogenic Stroke and Control Subjects

	Cryptogenic Stroke Patients (n = 69)	Control Subjects (n = 157)	p Value
Age, yrs	69.7 ± 8.4	67.0 ± 8.4	0.03
<60	10 (14)	30 (19)	
60–69	26 (38)	70 (45)	0.26
≥70	33 (48)	57 (36)	
Male	35 (50.7)	88 (56.1)	0.46
Body mass index, kg/m^2	27.2 ± 5.2	27.6 ± 4.8	0.55
Race/ethnicity			
White	9 (13.0)	23 (14.7)	
Black	23 (33.3)	50 (31.9)	0.94
Hispanic	37 (53.6)	84 (53.5)	
Risk factors			
Hypertension	55 (79.7)	105 (66.9)	0.05
Diabetes mellitus	26 (37.7)	36 (22.9)	0.02
Hypercholesterolemia	24 (35.8)	84 (53.5)	0.02
Current smoker	13 (20.0)	25 (16.2)	0.50
Smoking history	38 (55.9)	99 (63.1)	0.31
Coronary artery disease	10 (14.5)	33 (21.0)	0.25
Atrial fibrillation	3 (4.4)	7 (4.5)	0.96
Atrial septal abnormalities			
ASA	5 (7.3)	5 (3.2)	0.18
LSP	22 (31.9)	47 (29.3)	0.70

Values are mean ± SD or n (%).
Abbreviations as in Table 1.

risk factor. The interpretation of echocardiograms was blinded to the subjects' characteristics and risk factors, eliminating the possibility of ascertainment bias. The main limitation of our study is the relatively small sample size, which may have affected the statistical power to detect a significant risk associated with an LSP. However, with the observed OR of 0.98 (resulting from a 28.9% pouch prevalence rate in stroke patients and a 29.3% pouch prevalence rate in control subjects), a total of 20,400 subjects (1:1 ratio for case vs. control) would be needed to detect a significant difference with 80% power at the 0.1 significance level. The matching of cases and controls was inadequate to control for differences by age. However, age was entered as a potential confounder in all multivariable analyses. As in other case-control studies, our study has the limitation of possibly unequal distribution of prognostic variables between cases and controls, which may not have been completely adjusted for in the analysis. Because of the relatively advanced mean age of the population, we could not compare

Table 4. Predictors of Ischemic Stroke

	Univariable Model		Multivariable Model	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Age*	1.05 (1.02–1.08)	0.0002	1.05 (1.02–1.08)	0.0006
Male	0.83 (0.54–1.27)	0.383	1.14 (0.70–1.86)	0.60
Diabetes mellitus	2.92 (1.82–4.68)	<0.0001	3.47 (2.06–5.86)	<0.0001
Hypertension	2.79 (1.66–4.71)	0.0001	2.53 (1.41–4.53)	0.002
Hypercholesterolemia	0.65 (0.42–0.99)	0.046	0.60 (0.37–0.96)	0.03
Smoking history	0.74 (0.48–1.14)	0.17	0.72 (0.44–1.16)	0.18
Atrial fibrillation	2.86 (1.19–6.88)	0.02	2.18 (0.83–5.74)	0.12
LSP	0.98 (0.61–1.56)	0.93	1.09 (0.64–1.85)	0.76

*Age as a continuous variable. Univariable model for LSP: chi-square = 0.007, degrees of freedom = 1, p = 0.93, C statistic = 0.50; multivariable model: chi-square = 45.9, degrees of freedom = 8, p < 0.0001, C statistic = 0.73.
CI = confidence interval; LSP = left septal pouch; OR = odds ratio.

Table 5. Predictors of Cryptogenic Stroke

	Univariable Model		Multivariable Model	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Age*	1.04 (1.00–1.07)	0.03	1.04 (1.00–1.08)	0.03
Male	0.81 (0.46–1.42)	0.46	1.06 (0.56–2.01)	0.86
Diabetes mellitus	2.03 (1.10–3.75)	0.02	2.25 (1.14–4.44)	0.02
Hypertension	1.95 (0.99–3.82)	0.053	1.98 (0.94–4.16)	0.07
Hypercholesterolemia	0.49 (0.27–0.88)	0.02	0.50(0.27–0.93)	0.03
Smoking history	0.74 (0.42–1.32)	0.31	0.73(0.39–1.38)	0.34
Atrial fibrillation	0.97 (0.24–3.86)	0.96	0.48 (0.09–2.70)	0.41
LSP	1.13 (0.61–2.08)	0.70	1.41 (0.71–2.78)	0.33

*Age as a continuous variable. Univariable model for LSP: chi-square = 0.15, degrees of freedom =1, p = 0.70, C statistic = 0.51; multivariable model: chi-square = 17.45, degrees of freedom = 7, p = 0.03, C statistic = 0.69.
Abbreviations as in Tables 1 and 4.

different age groups (younger vs. older). Therefore, our results should not be extrapolated to a younger patient population.

CONCLUSIONS

Our results show no evidence of an association between the presence of an LSP and ischemic stroke. The possibility that the stroke risk may be increased in a subgroup of younger subjects with LSPs cannot be excluded by this study. Also, possible associated cofactors that may turn an LSP from an innocent bystander into a causative mechanism for stroke remain to be elucidated.

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Reprint requests and correspondence: Dr. Marco R. Di Tullio, Columbia University Medical Center, PH3-342, 622 West 168th Street, New York, New York 10032. *E-mail: md42@columbia.edu.*

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Key Words: left atrium ■ septal pouch ■ stroke ■ transesophageal echocardiography.