(St. Jude Medical) was applied with an intracoronary bolus administration of adenosine (80 μg in the left coronary artery and 40 μg in the right coronary artery) to induce maximal hyperemia. The jailed side branch was considered functionally significant when the FFR was ≤0.8.

Initially, 90 patients with 90 lesions were studied. However, 8 lesions were excluded due to poor quality of the reconstructed 3D OCT images. Therefore, 82 lesions in 82 patients were finally included in this study. A functionally significant stenosis was observed in 20 (24.4%) jailed side branches. Using receiver-operating characteristic curve analysis, the best cutoff value of the 3D OCT reconstructed side-branch MLA was 2.05 mm^2 for predicting a functionally significant stenosis (area under the curve: 0.81, 95% confidence interval: 0.71 to 0.91; $p < 0.001$; sensitivity: 71.0%; specificity 75.0%; positive predictive value: 54.5%; negative predictive value: 91.5%) (Figs. 1E and 1F).

In conclusion, 3D OCT had a modest ability to predict the functional significance for borderline lesions caused by a jailed side-branch ostium.

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ICE-Classification of Interatrial Septum Anatomy in Patients With R→L Shunt

Right-to-left (R-to-L) shunt caused by patent foramen ovale (PFO) is a dark field for interventionalists, particularly after the conflicting results from the most recent trials regarding PFO transcatheter closure. It seems that the confusing results (negative in the Closure I [Closure or Medical Therapy for Cryptogenic Stroke With Patent Foramen Ovale] trial [1] and slightly positive in the RESPECT [Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment] and PC [Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism] [2,3] trials) might be related to patient selection, in particular anatomical inclusion/exclusion criteria and device choice. We tried to clarify the relationships of different anatomical subtypes and the association of anatomical characteristics of the interatrial septum with risk of recurrent paradoxical embolism and shunt grade.

We retrospectively reviewed the medical and instrumental data of 520 consecutive patients (mean age 44.0 ± 15. 5 years; 355 females) who had been referred to our center over a 10-year period (February 2003 to February 2013) for R-to-L shunt catheter-based closure. Inclusion criteria for percutaneous closure of PFO included the following: 1) a concurrent permanent or shower or curtain shunt pattern on transcranial Doppler with Valsalva maneuver; 2) positive (single or multiple ischemic foci) cerebral magnetic resonance imaging; 3) previous neurologically confirmed stroke or transient ischemic attack; and 4) moderate or large PFO on transesophageal echocardiography. The hospital ethical board approved the study, and written informed consent was obtained from all patients enrolled in the study.

In all patients, the attempt at transcatheter closure was preceded by a mechanical 9-F, 9-MHz, 360° scan probe (UltraICE, EP Technologies, Boston Scientific Corporation, San Jose, California) intracardiac echocardiography. This study was conducted in 2 projections, measuring diameters of the oval fossa, the entire atrial

Table 1. Distribution of Demographic, Clinical, and Functional Parameters Among the 4 Anatomical Subtypes

	Type 1 (n = 71 [13.7%])	Type 2 (n = 232 [44.6%])	Type 3 (n = 175 [33.6%])	Type 4 (n = 42 [8.1%])	p Value	Total (N = 520)
Age <45 yrs	54 (76.0)	135 (58.2)	102 (58.3)	21 (50.0)	<0.0001	312 (61.7)
Female	46 (64.8)	168 (72.4)	119 (68.0)	22 (55.5)	0.0752	355 (68.3)
Hypertension	24 (33.8)	90 (38.8)	36 (20.5)	6 (14.3)	<0.0001	156 (30.0)
CoA	23 (32.3)	58 (25.0)	66 (37.7)	14 (33.3)	0.0955	162 (31.1)
Curtain shunt	28 (39.4)	123 (53.0)	108 (61.7)	30 (71.4)	0.0068	289 (55.6)
Permanent shunt	25 (35.2)	117 (50.4)	138 (78.8)	21 (50.0)	<0.0001	301 (57.8)
Recurrent CIE	34 (47.8)	138 (59.4)	128 (73.1)	21 (50.0)	<0.0001	321 (61.7)
Multiple CIF RMi	30 (42.2)	121 (52.1)	118 (67.4)	28 (66.6)	<0.0001	297 (57.1)

Values are n (%).
CIE = cerebral ischemic event; CIF = cerebral ischemic foci; CoA = coagulation abnormalities (deficiency of anti-thrombin III, C, S, or factor V Leiden or homozygotic mutation methylenetrahydrofolate reductase or antiphospholipid or anticardiolipin antibodies); RMi = resonance magnetic imaging.

septum length, and rims and thickness with electronic caliper edge-to-edge (4). Four main features were used to analyze patients: 1) diameter of the fossa ovalis (FO); 2) presence and length of the channel; 3) presence and degree of atrial septal aneurysm (ASA), following the classification of Olivares et al. (5); and 4) rim thickness. We also analyzed the presence of Eustachian valve and Chiari's network. We considered eventual additional fenestrations within the fossa as a functional subtype of PFO, despite that, anatomically, they should be considered as secundum atrial septal defects.

Thus, combinations of interatrial septum anatomical features were classified into 4 main anatomical subgroups: type 1, small FO, no ASA, short channel, normal rims; type 2, small FO, no ASA, long channel, normal or hypertrophic rims; type 3, large FO, 4 to 5 ASA, short channel, normal or hypertrophic rims; and type 4, large FO, 3 to 5 ASA, multifenestrated, short channel, normal rims (Table 1).

FO diameter ≤20 mm was found to be statistically correlated to the presence of a tunnelized PFO ($r = 0.91$, $p < 0.001$), whereas FO diameter >25 mm was associated with the presence of ASA ($r = 0.88$, $p < 0.001$) and a linear correlation between diameter of the FO and ASA severity (the larger the fossa, the more severe the ASA) ($r = 0.90$, $p < 0.001$). Type 3 anatomical subtype (odds ratio: 4.1 [95% confidence interval: 1.5 to 8.0]; $p < 0.001$) and type 2 + Eustachian valve (odds ratio: 4.3 [95% confidence interval: 1.6 to 9.0]; $p < 0.001$) were the strongest predictors of recurrent ischemic events before transcatheter closure.

Our study suggests that the anatomy of the interatrial septum associated with R-to-L shunt is more complex than commonly thought. The combination of the varieties of such anatomical components identifying 4 main anatomic subtypes may help in better clarifying the pathophysiology of paradoxical embolism, which is unlikely to be dominated by 1 factor only, such as ASA, PFO tunnel, or fenestrations. Intriguingly, our data suggest that the FO diameter plays a role in determining the presence of both tunnelized PFO, when the oval fossa is small (<20 mm), and the presence of aneurysm, when the fossa is large (≥20 mm).

In conclusion, our study showed that in a "real-world" interatrial septum, anatomy greatly differs among patients with R-to-L shunt. The clinical significance of each anatomical pattern seems different: a device closure might be advisable in patients with high-risk anatomical patterns whereas a medical strategy might be adopted in the others.

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Perflutren-Based Echocardiographic Contrast in Patients With Right-to-Left Intracardiac Shunts

Use of second-generation perflutren-based echocardiographic contrast agents (perflutren) is currently contraindicated in patients with known right-to-left, bidirectional, or transient right-to-left intracardiac shunts (intracardiac shunts) according to the U.S. Food and Drug Administration. This contraindication is primarily a result of concerns related to neurological complications and/or systemic embolism from animal data describing entrapment of perflutren lipid microspheres (>5 μm in diameter) within small arterioles and capillaries in skeletal muscles after intra-arterial injection. To date, no definitive evidence demonstrates patient safety concerns from perflutren use in humans with intracardiac shunts. We sought to evaluate the association between perflutren use and adverse events in these patients.

A retrospective cohort study was performed to evaluate the association of perflutren use (Definity, Lantheus Medical Imaging, North Billerica, Massachusetts; Optison, GE Healthcare, Milwaukee, Wisconsin) and adverse events in patients with and without known intracardiac shunts using the echocardiography database at Hennepin County Medical Center (Minneapolis, Minnesota). The study was approved by the institutional review board. Patients with known intracardiac shunts (diagnosed using right heart contrast [agitated saline/50% dextrose] or color flow Doppler) were identified from the database. Per laboratory protocol, perflutren was not used in patients with cyanotic congenital heart disease. Documentation of all adverse events reported by laboratory personnel within a 30-min interval after perflutren administration was identified. Individual patient charts were reviewed to confirm clinical events in all patients who experienced adverse events. All adverse events were further categorized as primary or secondary. Primary events were defined as neurological (stroke/transient ischemic attack) and/or systemic embolism. Secondary events, collectively referred to as complement activation-related pseudoallergy (CARPA), included angioedema, bronchospasm, hypotension, hypoxemia, low back pain, and urticaria. Fisher exact test was used to evaluate statistical significance.

From February 1, 1998, through November 30, 2012, 39,020 echocardiograms were performed using perflutren (Definity: 34,598; Optison: 4,422). An intracardiac shunt was not identified