



# Diagnosis of Secondary Source of Right-to-Left Shunt With Balloon Occlusion of Patent Foramen Ovale and Power M-Mode Transcranial Doppler

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**Objectives** We sought to assess the prevalence of secondary right-to-left circulatory shunt (RLS) in patients undergoing transcatheter closure of patent foramen ovale (PFO) as detected by power M-mode transcranial Doppler (TCD) and intracardiac echocardiography.

**Background** Prevalence of residual RLS in late follow-up after PFO closure may be as high as 34%. Other cardiac and noncardiac sources of RLS may coexist and obscure PFO closure evaluation.

**Methods** Eighty-eight patients who underwent transcatheter PFO closure to prevent recurrent paradoxical cerebral embolism between June 2005 and December 2006 were evaluated for a secondary source of RLS. Before device deployment, a sizing balloon was inflated in the PFO tunnel and agitated saline contrast was injected into the inferior vena cava. Clinically significant secondary RLS was defined as >10 embolic tracks on TCD at rest or immediately after calibrated (40 mm Hg), sustained (10 s) respiratory strain, with corresponding negative color-flow Doppler. Late residual RLS was evaluated in all patients with TCD and transthoracic echocardiography (mean: 192 days; 95% confidence interval [CI]: 161 to 223 days).

**Results** The sample (n = 84) was 59% female, age  $49 \pm 14$  years. Seventeen patients (20%; 95% CI: 11.7 to 28.8) had secondary RLS during balloon occlusion. At late follow-up (n = 66), 13 of 14 (93%) patients with secondary RLS and 23 of 52 (44%) patients without secondary RLS had residual RLS (p = 0.002).

**Conclusions** This is the first report to systematically assess the prevalence of secondary RLS in patients undergoing PFO closure. Residual RLS detected by TCD may be due to secondary RLS, which may have implications for clinical outcomes. (J Am Coll Cardiol Intv 2009;2:561-7) © 2009 by the American College of Cardiology Foundation

Paradoxical cerebral embolism is presumed to be the leading cause of cryptogenic ischemic stroke in patients with patent foramen ovale (PFO) age <50 years. Approximately 70,000 strokes are attributed to PFO annually (1). The causal mechanism of stroke among persons with PFO is unclear, but may be related to the transient shunting of blood from the right to left atrium across the PFO, thus permitting small thrombi or other substances of venous origin to bypass pulmonary filtration and enter the systemic circulation (2).

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Transcatheter closure of PFO is associated with a low incidence of recurrent stroke. In an early meta-analysis (3), the 1-year recurrence rate for neurological events was 0% to 4.9% for PFO closure and 3.8% to 12.0% for medical therapy. With improved closure devices and longer duration of follow-up, the rate of recurrent stroke following PFO closure ranges from 0% to 3.4% per year (4–6). In our

#### Abbreviations and Acronyms

**ASD** = atrial septal defect

**ET** = embolic track(s)

**ICE** = intracardiac  
echocardiography

**PAVM** = pulmonary  
arteriovenous malformation

**PFO** = patent foramen ovale

**RLS** = right-to-left shunt

**TCD** = power M-mode  
transcranial Doppler

**TTE** = transthoracic  
echocardiography

experience, the overall recurrent stroke rate in patients who had PFO closure for prevention of recurrent stroke was 3.4% during a mean follow-up of  $568 \pm 364$  days; for patients age  $\leq 55$  years, the rate was 1.4% (7).

In recent reports, the rate of residual right-to-left shunt (RLS) following PFO closure may be as high as 34% in late follow-up (7,8). Residual RLS has been associated with recurrent stroke following PFO closure (hazard ratio: 6.9, 95% confidence interval [CI]: 1.3 to

36.9;  $p < 0.03$ ) (9). Cardiac and noncardiac sources of circulatory shunt (e.g., pulmonary arteriovenous malformation [PAVM] or atrial septal defect [ASD]) may coexist with PFO and obscure the evaluation of residual RLS following transcatheter PFO closure; however, there are no published population-based studies on the prevalence of coexisting PAVM or ASD in patients with PFO.

The purpose of the present study was to obtain preliminary findings on the prevalence of secondary source of RLS in patients with PFO at the time of transcatheter PFO closure using a compliant sizing balloon, intracardiac echocardiography (ICE), and power M-mode transcranial Doppler (TCD). We hypothesized that patients who had positive TCD during balloon occlusion of the PFO, suggestive of a noncardiac source of secondary RLS, would have a higher rate of residual RLS immediately following device deployment and in late follow-up as compared with those who had negative TCD during PFO balloon occlusion.

## Methods

This single-center, prospective study was approved by the Swedish Medical Center Institutional Review Board and was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki. The target population included patients who underwent transcatheter PFO closure at Swedish Medical Center between June 2005 and December 2006. A consecutive, nonrandom technique was used to select the sample. Eligibility criteria for transcatheter PFO closure included a presumed paradoxical embolic event; evidence that RLS could be provoked, confirmed by TCD and transthoracic echocardiography (TTE) or transesophageal echocardiography; and probe patency of the septal tunnel during catheterization.

Detection of embolic tracks (ET) was performed using the PMD100 transcranial Doppler platform (Spencer Technologies, Seattle, Washington) in the Swedish Medical Center Cardiac Catheterization Laboratory. A PMD100 2-MHz ultrasound probe was mounted and stabilized over each temporal bone using the Marc 600 head frame (Spencer Technologies). Patients were placed in a supine position with the head raised 30° and measures were taken to avoid neck rotation or flexion. After obtaining adequate bilateral temporal bone window signals, all patients had at least 2 contrast injections during TCD evaluation using methods described by Spencer et al. (10). Each contrast injection consisted of 9 ml normal saline, 1 ml air, and a small amount of the patient's blood manually agitated between 2 syringes for 10 s and injected into the inferior vena cava in the cardiac catheterization laboratory or in an antecubital vein for follow-up evaluation (10,11). The first injection was performed during normal respiration (rest). The second injection was performed immediately before performance of calibrated respiratory strain. Each patient was instructed to blow into a mouthpiece attached to a manometer until 40 mm Hg pressure was achieved and maintained for 10 s. Embolic tracks for both injections were counted for 1 min after the microbubbles reached the pulmonary artery (10).

Intracardiac echocardiography was performed during PFO closure (Acuson AcuNav, Siemens, San Diego, California) to evaluate PFO tunnel length, balloon-stretch diameter, and the presence of coexisting atrial septal aneurysm and/or ASD (12). A compliant, conforming sizing balloon was used to assess PFO diameter and to guide device size selection. Balloon inflation was completed when the PFO tunnel was completely occluded and a small waist was visible on ICE. The inflated balloon waist diameter was measured with the aid of calibrations on the sizing balloon. Septal tunnel length was measured as the distance between right and left atria. Atrial septal characteristics were evaluated post-procedurally by a single cardiologist (K.A.K.) with expertise in echocardiography. Atrial septal aneurysm was defined as a localized protrusion of the fossa ovalis, with a

base width  $\geq 15$  mm and mobile septal excursion into the left or right atrium  $\geq 10$  mm (13). Atrial septal defect was defined as a predominant left-to-right shunt at rest, based on color-flow Doppler interrogation. Patients who were diagnosed with coexisting ASD were excluded from the analysis. After the procedure, antiplatelet therapy consisted of clopidogrel 75 mg for 3 months and aspirin 325 mg for  $\geq 6$  months.

To evaluate the presence of secondary RLS, a novel procedure not previously described was employed. During PFO balloon inflation, color-flow Doppler in conjunction with ICE was used to confirm complete occlusion of the PFO tunnel, at rest and during respiratory strain. If color-flow Doppler showed continual RLS during PFO balloon inflation, the balloon was repositioned and/or reinflated to occlude the tunnel. If color-flow Doppler confirmed the absence of RLS during balloon inflation, 10 ml of agitated saline contrast was injected during normal respiration and immediately (5 s) prior to respiratory strain. Complete balloon occlusion was achieved in all patients. No patients were excluded due to positive color-flow Doppler during balloon occlusion. Right-to-left shunt was considered positive if ET were detected at either rest or following respiratory strain. A clinically significant secondary RLS was defined as  $>10$  ET at rest or following respiratory strain during balloon occlusion of the PFO;  $<10$  ET constituted the absence of a clinically significant secondary RLS. Although quantitation of ET ranged from 0 to 301, 301 indicating microemboli too numerous to count (10), a conservative periprocedural definition of secondary RLS was adopted for the study to avoid false positive findings.

Patients were divided into 2 groups, based on the presence or absence of secondary RLS during PFO balloon occlusion. The TCD evaluation was performed at 3 separate time points (10 cc agitated saline injection at rest and following respiratory strain), reported in this analysis as: 1) during balloon occlusion of the PFO to assess for presence of secondary RLS; 2) immediately following septal occluder device deployment to assess device placement and presence of residual RLS; and 3) in late follow-up to determine presence of residual RLS after closure. In late follow-up, TTE was used in conjunction with TCD to rule out a cardiac source of residual RLS. For the purpose of this study, size of residual RLS in late follow-up was based on the number of ET during TCD following respiratory strain and arbitrarily classified as small (1 to 10 ET), moderate (11 to 100 ET), and large ( $>100$  ET).

**Statistical analysis.** Descriptive statistics were performed for demographic and echocardiographic characteristics, duration of follow-up, recurrent events, and RLS. Data are presented as mean  $\pm$  SD, mean and 95% CI for continuous data, or n (%) for categorical data. Comparisons between groups with and without secondary RLS were performed for

demographic, comorbidity, and TCD data by chi-square or Fisher exact test for categorical data; continuous data were compared using independent sample *t* tests or Mann-Whitney *U* tests. Levene test was used to assess equality of variances for parametric tests. Linear regression analysis was performed to assess predictors of residual RLS at late follow-up. Assumptions of normality, linearity, and equality of variances were assessed by examining histograms and scatter plots of predicted and residual values. Post hoc power analysis for the primary hypothesis was performed using noncentral chi-square analysis. All statistical analyses were performed using SPSS version 15.0 and SamplePower Version 2.0 (SPSS Inc., Chicago, Illinois). The threshold for statistical significance for all tests was set at  $\alpha = 0.05$ , 2-tailed.

## Results

**Patient characteristics.** Eighty-eight of 140 (63%) consecutive patients were referred to the Swedish Medical Center Cardiac Catheterization Laboratory and underwent PFO closure between June 2005 and December 2006 and were evaluated for secondary source of RLS. All patients underwent PFO closure to prevent recurrent cerebrovascular events due to presumed paradoxical embolism. Four patients (5%) were excluded from the analysis due to coexisting ASD; therefore, 84 patients were included in the final sample. Four additional patients (5%) did not have TCD evaluation immediately following device deployment, which represented a protocol deviation. Eighteen patients (21%) were lost to follow-up and did not have TCD/TTE evaluation after closure. Therefore, analysis in late follow-up was based on  $n = 66$ .

During balloon occlusion of the PFO ( $n = 84$ ), 17 (20%; 95% CI: 11.7 to 28.8) patients had a positive TCD (ET: 11 to 301) with simultaneous negative color-flow Doppler, suggestive of a clinically significant noncardiac source of secondary RLS. Of the 18 lost to follow-up, 3 (17%) had a secondary source of RLS. The demographic and procedural characteristics of groups with and without significant secondary RLS are listed in Table 1. The overall sample was 58% female and 83% Caucasian, age  $49 \pm 14$  years. The 18 patients lost to follow-up were 44% female, 89% Caucasian, and age  $53 \pm 14$  years. There were no differences in baseline characteristics for patients with and without follow-up. Periprocedurally, patients with PFO and secondary RLS had a greater number of ET at rest and following respiratory strain than patients without secondary RLS, although the differences were not statistically or clinically significant ( $p = 0.3$  and  $p = 0.1$ , respectively). Furthermore, patients with secondary RLS had a higher prevalence of atrial septal aneurysm than patients without secondary RLS did, although this also was not statistically significant (24% vs. 18%, respectively;  $p = 0.7$ ). On average, patients with

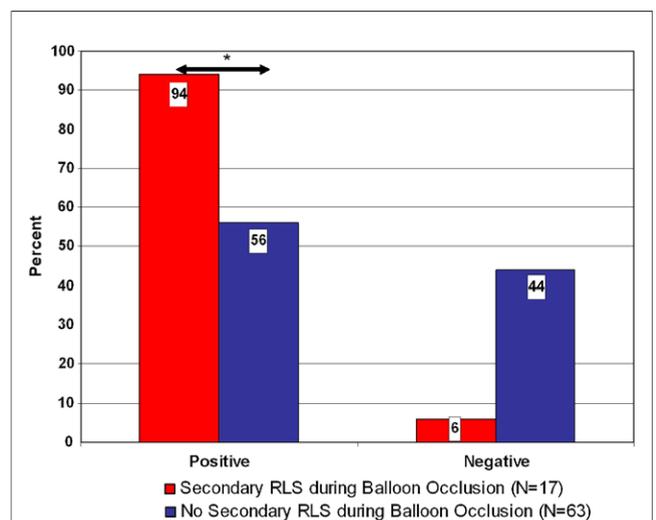
Table 1. Demographic and Procedural Characteristics of Groups With and Without Secondary RLS Following Balloon Occlusion (n = 84)		
Characteristic	Patients With Secondary RLS (n = 17)	Patients Without Secondary RLS (n = 67)
Age, yrs	46 ± 13	49 ± 14
Females	10 (59%)	39 (58%)
Caucasian	16 (94%)	54 (81%)
Number of strokes before PFO closure	1.3 ± 0.6	1.2 ± 0.5
Number of transient ischemic attacks before PFO closure	1.4 ± 0.5	1.6 ± 0.6
Migraine history	7 (41%)	26 (41%)
Coexisting atrial septal aneurysm	4 (25%)	12 (18%)
Embolic tracks on TCD at rest, pre-closure	148 ± 139	116 ± 117
Embolic tracks on TCD after calibrated respiratory strain, pre-closure	269 ± 73	235 ± 108
PFO balloon diameter, mm	13.9 ± 4.3	11.4 ± 3.4 (p = 0.013)
PFO tunnel length, mm	12.3 ± 2.6	11.0 ± 3.0
Device*		
CardioSEAL	15 (88%)	61 (87%)
Amplatzer	1 (6%)	6 (9%)
Helex	1 (6%)	0
Device size, mm		
23	4 (24%)	25 (37%)
28	5 (29%)	28 (42%)
33	5 (29%)	6 (9%)
Other	3 (18%)	8 (12%)

\*CardioSEAL (NMT Medical, Boston, Massachusetts); Amplatzer (AGA Medical, Golden Valley, Minnesota); Helex (W.L. Gore, Flagstaff, Arizona).  
PFO = patent foramen ovale; RLS = right-to-left shunt; TCD = power M-mode transcranial Doppler.

secondary RLS had larger PFO waist diameters than those without secondary RLS ( $14 \pm 4$  mm vs.  $11 \pm 3$  mm, respectively;  $p = 0.013$ ); however, the prevalence of comorbid conditions and other septal characteristics were similar between the groups with and without secondary RLS

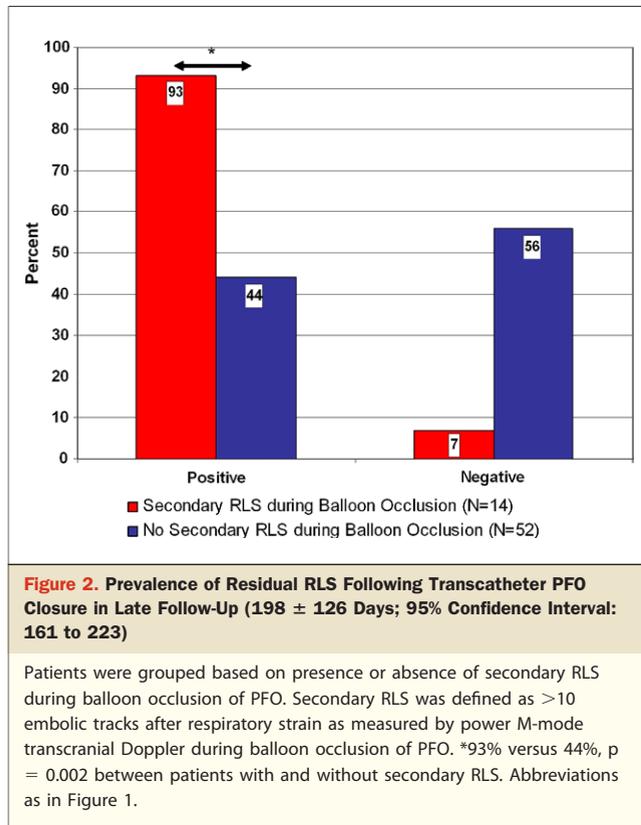
Transcranial Doppler assessment of RLS was performed immediately after septal occluder device deployment in 80 (95%) patients; due to protocol deviation, 4 patients did not receive TCD evaluation following device deployment, none of whom had secondary RLS. Patients who had secondary RLS had a higher proportion of residual RLS (ET: 1 to 301) immediately following device deployment than those who did not have secondary RLS (94% vs. 56%, respectively;  $p = 0.004$ ) (Fig. 1).

During TCD evaluation at late follow-up (mean: 192 days, 95% CI: 161 to 223 days;  $n = 66$ ), 36 (55%) patients in the sample had residual RLS (1 to 301 ET). In comparing groups with and without secondary RLS, 13 of 14 (93%) patients who had secondary RLS during PFO balloon occlusion had residual RLS at late follow-up. In contrast, the remaining 23 of 52 (44%) patients without secondary RLS during balloon occlusion had a much lower prevalence of residual RLS at late follow-up (93% vs. 44%;  $p = 0.002$ ) (Fig. 2). The difference between the number of ET at rest and following respiratory strain was higher in the group



**Figure 1. Prevalence of Residual RLS Immediately Following PFO Device Deployment**

Patients were grouped based on presence or absence of secondary RLS during balloon occlusion of PFO. Secondary RLS was defined as  $>10$  embolic tracks, at rest or after respiratory strain, as measured by power M-mode transcranial Doppler during balloon occlusion of PFO. \*94% versus 56%,  $p = 0.004$  between patients with and without secondary RLS. PFO = patent foramen ovale; RLS = right-to-left shunt.



with secondary RLS ( $105 \pm 131$ ;  $p = 0.01$ ) than in the group without secondary RLS ( $43 \pm 85$ ;  $p = 0.001$ ) in late follow-up. For the observed effect size (0.49; 95% CI: 0.030 to 0.68) of secondary RLS on late residual RLS, and sample sizes of 14 and 52 for the 2 groups, the study had 97% power to detect a statistically significant difference ( $\alpha = 0.05$ , 2-tailed).

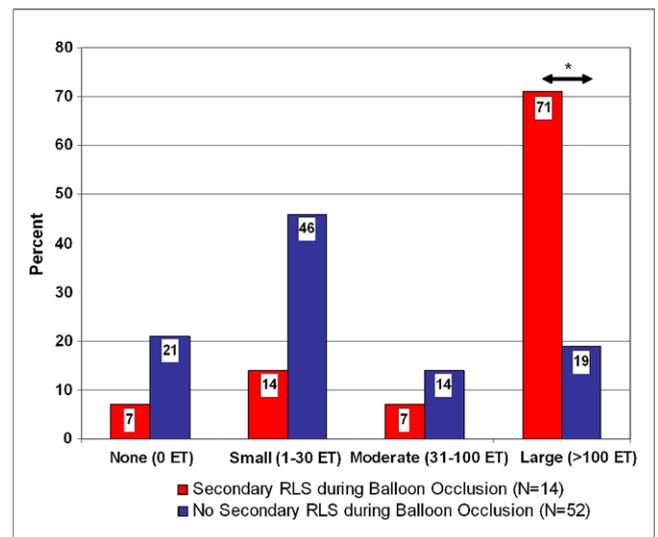
Overall, 30% (20 of 66) of patients in the sample had large residual RLS (101 to 301 ET) at late follow-up. In comparing groups, 71% (10 of 14) of patients with secondary RLS during PFO balloon occlusion had large residual RLS versus 19% (10 of 52) of patients without secondary RLS ( $p < 0.0001$ ) (Fig. 3). Regression analysis revealed that: 1) PFO balloon waist diameter; and 2) the number of ET detected on TCD during balloon occlusion of PFO (either at rest or following respiratory strain) were predictive of residual RLS following transcatheter PFO closure (balloon waist:  $\beta = 0.34$ ,  $p = 0.002$ ; ET during balloon occlusion:  $\beta = 0.43$ ,  $p < 0.001$ ).

## Discussion

The primary objective of this study was to gather preliminary data on the prevalence of secondary RLS in patients undergoing transcatheter PFO closure for prevention of recurrent cerebrovascular events. Twenty percent (95% CI: 11.7 to 28.8) of patients referred for PFO closure had a

secondary source of RLS during balloon occlusion before device implantation as diagnosed by contrast-enhanced TCD and ICE. To our knowledge, this is the first study to systematically evaluate the prevalence of secondary source of RLS periprocedurally in patients with PFO. The combination of balloon occlusion of the PFO tunnel, ICE, and TCD allowed us to indirectly assess noncardiac sources of RLS before septal occluder device deployment. The combination of TCD and ICE allowed optimal detection of RLS without the sedation required for transesophageal echocardiography (14), which can limit a patient's ability to adequately perform respiratory strain (15) and may result in a false negative result. The use of ICE with color-flow Doppler allowed for direct visualization of the atrial septum to rule out coexisting ASD and inadequate balloon occlusion of the PFO.

Although the association between PFO and cryptogenic stroke remains controversial, the goal of PFO closure is to reduce or eliminate the risk of recurrent paradoxical embolism by eliminating RLS. Late residual RLS is an independent risk factor of recurrent stroke following PFO closure (9). Depending on the modality used to detect RLS, the prevalence of late residual RLS can be as high as 34% following transcatheter PFO closure (7,8). To adequately evaluate the "technical" success of PFO closure, it is important to identify other noncardiac secondary sources of RLS before device implantation.



**Figure 3. Size of Residual RLS, as Assessed by ET With TCD, in Late Follow-Up After Transcatheter PFO Closure (192 ± 126 Days; 95% Confidence Interval: 161 to 223)**

The size of late residual RLS was significantly different between patients who had secondary RLS during balloon occlusion of PFO ( $p = 0.003$ ). The proportion of large residual RLS was significantly greater in patients who had secondary RLS during balloon occlusion. \*71% versus 19%,  $p < 0.0001$  for the presence of large residual RLS between patients with and without secondary RLS. ET = embolic tracks; TCD = power M-mode transcranial Doppler; other abbreviations as in Figure 1.

The results of this study suggest that a secondary source of RLS may contribute to the high prevalence of late residual RLS after transcatheter PFO closure. Patients who had secondary RLS during balloon occlusion of PFO had a significantly higher rate of residual RLS immediately following PFO device deployment compared with those without secondary RLS (94% vs. 56%). More importantly, these differences persisted at late follow-up (93% and 44%). The finding that 44% of patients in the present study who did not have secondary RLS had late residual RLS following PFO closure is consistent with our previously published findings of 34% residual RLS at  $568 \pm 364$  days after PFO closure (7). The secondary source of RLS was not assessed in this cohort.

In follow-up, concurrent TCD and TTE evaluation was used to diagnose residual RLS and distinguish between cardiac and noncardiac sources of RLS. The TCD modality used in this study is more sensitive than transesophageal echocardiography to detect RLS when compared with anatomical findings in the catheterization laboratory (98% vs. 91%) (10). Use of TCD may partially explain our relatively high overall rate (55%) of residual RLS at late follow-up of 192 days (95% CI: 161 to 223 days). The high rate of residual RLS may be device-specific, as nearly 90% of all patients were implanted with CardioSEALs (NMT Medical, Boston, Massachusetts).

The study was adequately powered to detect statistically and clinically significant differences in late residual RLS between the groups with and without a secondary source of RLS. In late follow-up, 30% (20 of 66) of patients in the sample had large residual RLS (101 to 301 ET); 71% (10 of 14) of patients with secondary RLS during PFO balloon occlusion versus 19% (10 of 52) of patients without secondary RLS ( $p < 0.001$ ). This is an important finding that reinforces the need to assess the presence of secondary source of RLS before transcatheter PFO closure.

The association between PFO balloon diameter and residual RLS is of concern. The morphology of PFO ranges from the "simple" to the large incompetent "valve" with or without an atrial septal aneurysm. Whether these larger openings represent a single developmental abnormality or are part of a constellation of abnormalities during embryogenesis should be considered in future studies based on the present data. In unpublished data, our group has previously found nonsignificant correlations between balloon diameter of PFO and pre-closure size of RLS as measured by TCD and ET quantification at rest or following respiratory strain ( $n = 84$ ;  $r = 0.09$  and  $r = 0.16$ , respectively, both  $p$  values  $>0.05$ ).

Pulmonary arteriovenous malformation is the most likely cause of secondary RLS not detectable by ICE, although this was not confirmed with pulmonary angiography. Non-cardiac sources of RLS such as PAVM have been associated with cerebrovascular events (16,17), and the presence of multiple PAVMs significantly increases the risk of cerebro-

vascular events (odds ratio: 4.5; 95% CI: 1.47 to 14) (18). Published case reports have documented the coexistence of noncardiac source of RLS with PFO (19,20); however, large case series are lacking in the literature. Although pulmonary angiography is the gold standard for diagnosing PAVM, contrast-enhanced TTE has been shown to have high positive predictive value for normal respiration ( $n = 12$  of 12) (21). The timing of appearance of contrast microbubbles on TTE may not be associated with the presence of PAVM on computed tomography (21,22). Undiagnosed coexisting ASD can also result in residual RLS following PFO closure; however, the use of color-flow Doppler interrogation in the present study reduced the probability of an incorrect ASD diagnosis (23).

The results of the present study are limited in their generalizability to the larger PFO population. This study was limited by the small number of patients and the high number of patients (21%) lost to follow-up. Swedish Medical Center is a regional referral center, and many of these patients lived in outlying areas or other states and were unable to return for follow-up. Nevertheless, post hoc analysis showed that this study had adequate statistical power (0.97) to test the effect of secondary source of RLS on late residual RLS.

The short duration of follow-up (192 days, 95% CI: 161 to 223 days) is of concern; however, the definition of "late follow-up" is inconsistent across PFO closure trials. The MIST (Migraine Intervention with STARFlex Technology) trial (STARFlex, NMT Medical) used 6 months for final TTE follow-up to assess PFO closure (24). In a previous retrospective analysis (7), 78% of patients showed no significant change in degree of RLS between 1 and 6 months, and 82% had no significant change in degree of RLS between 6 and 12 months following PFO closure. Pulmonary angiography was not performed to verify presence of PAVM. Selection bias may have been a factor in the results obtained, as all patients underwent PFO closure for prevention of recurrent cerebrovascular events. Clinical sequelae (stroke, transient ischemic attack) were not assessed following PFO closure, and the study was not sufficiently powered to detect a difference in the incidence of recurrent stroke in patients with and without secondary source of RLS. The purpose of our study was to obtain preliminary findings on the prevalence of secondary sources of RLS in patients with PFO at the time of transcatheter PFO closure using a compliant sizing balloon, ICE, and TCD. We did not, however, collect clinical outcomes data as part of this study. We have previously published findings on the association between residual RLS following PFO closure and clinical sequelae. In this retrospective analysis, age at the time of PFO closure was the only significant univariate predictor of recurrent stroke ( $\beta = 0.076$ ,  $p = 0.03$ ). There were no significant differences in the risk for recurrent stroke with

respect to final closure status, sex, history of multiple strokes, coexisting atrial septal aneurysm, or hypertension (7).

## Conclusions

The results of this prospective, preliminary study suggest that balloon occlusion, ICE, and TCD can be used during transcatheter PFO closure to detect secondary sources of RLS such as PAVM. Patients who had secondary RLS were more likely to have late residual RLS. Ongoing PFO studies utilizing these diagnostic modalities (especially TCD) to determine closure status need to factor the current findings in their design. In addition, future research needs to be conducted to assess the incidence of recurrent clinical sequelae following PFO closure in patients diagnosed with a secondary source of RLS at the time of PFO closure.

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