# Follow-up of residual shunt after patent foramen ovale closure

Orzan F, Liboni W, Bonzano A, Molinari F, Ribezzo M, Rebaudengo N, Grippi G, Negri E. Follow-up of residual shunt after patent foramen ovale closure.

*Objectives* – Transesophageal echocardiography (TEE) is usually recommended in the evaluation of the patent foramen ovale (PFO). Our goal is to confirm the efficacy of contrast-enhanced transcranial Doppler (ce-TCD) in detecting residual significant right-to-left shunts (RLS) after PFO percutaneous closure. *Materials and methods* – Sixty-eight patients with a previous transient ischemic attack, stroke and a large PFO were investigated for residual RLS after percutaneous closure. *Results* – Assuming TEE as the gold standard, the sensitivity and negative predictive value of ce-TCD was 100%, whereas the specificity was 75.8% and the positive predictive value was 28%. *Conclusions* – ce-TCD appears to be the preferable technique to identify subjects with significant residual shunts after percutaneous closure of a PFO. In follow-up, if ce-TCD is negative, no further examination may be necessary; whereas if ce-TCD shows a residual shunt, it is advisable to perform a TEE investigation.

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## Introduction

Percutaneous closure of patent foramen ovale (PFO) is advocated to prevent recurrences of cerebrovascular ischemic events (1), migraine attacks (2), and to protect divers from the risk of gas emboli to the brain (3). The issue of PFO closure in symptomatic patients is still debated. This enforces the need for an accurate patient monitoring after percutaneous PFO closure. In fact, recurrent thromboembolic events after percutaneous closure of the PFO have been linked to the persistence of a communication between the atria (4, 5). A systematic evaluation of the effective sealing is therefore warranted, and transesophageal echocardiography (TEE) is usually recommended (6).

Contrast-enhanced transcranial Doppler (ce-TCD) is comparable with contrast TEE for detecting right-to-left shunts (RLS) as a result of PFO (7, 8). Anzola et al. (9) have proposed that ce-TCD may be superior for detecting residual significant shunts after PFO closure.

We report our results of the evaluation of residual RLS through the interatrial septum (IAS) after percutaneous closure by ce-TCD, as compared with contrast TEE, to investigate the relative merit of the two techniques.

## Materials and methods

### TEE technique

TEE was performed according to standard practice guidelines. Esophageal intubation was performed with the patient in the fasting state and in the left lateral decubitus position, after premedication with topical anesthesia and sedation, as clinically indicated. A commercially available ultrasound device (HP Sonos 1500/2500 equipped with an OmniPlane probe; Philips Medical, Bothel, WA, USA) was used for cardiac imaging. The heart and thoracic aorta were scanned for the presence of potential embolic sources (left atrial or ventricular thrombi, endocardial vegetations, and aortic plaques).

The IAS was explored primarily in the transverse midesophageal four-chamber view and the longitudinal biatrial/bicaval view. An aneurysm of the interatrial septum (ASA) was defined as the protrusion of the IAS of more than 10 mm beyond the plane of the IAS (10) or as a phasic

excursion of the IAS during the respiratory cycle of more than 10 mm in total amplitude.

Color Doppler helped to detect a shunt through the IAS, and to identify multiple sites, but the final diagnosis of RLS rested on the contrast injection technique. Briefly, 10 ml of a solution consisting of agitated saline (5 ml), blood (4 ml), and air (1 ml) was injected into a brachial vein at rest and during the strain phase of the valsalva maneuver (VM); the patients were asked to 'let go' only when the right atrium was fully opacified.

Criteria for patency of the foramen ovale were based on finding contrast in the left atrium (LA) within three cardiac cycles after full right atrium opacification, and were categorized as follows: absent (when no microbubbles were seen in the LA either at rest or after Valsalva); not significant (when less than 10 microbubbles passed into the LA after VM); moderately positive (when 10–20 microbubbles passed in the LA only after VM); strongly positive (when more than 20 microbubbles were detected in the LA after valsalva or if microbubbles were observable at rest). Strongly positive results were deemed indicative of a large PFO (11, 12).

On TEE, 23 patients (34%) had an ASA; the shunt was large in 61 (90%); 62 (91%) had either a large shunt or an ASA.

### ce-TCD technique

By means of a DWL Multi-Dop machine (Compumedics, Singen, Germany), a bilateral ce-TCD with two 2-MHz probes installed on a special headset (LAM rack) was performed. After a basal examination of the anterior, middle, and posterior cerebral arteries by TCD, the ce-TCD test was performed in three steps:

1. VM alone.
2. *Contrast injection alone*: 10 ml of a mixture of agitated saline (5 ml), blood (4 ml), and air (1 ml; same composition as in TEE examinations) was injected into the right antecubital vein while the Doppler signal from both the right and the left middle cerebral artery (MCA) was recorded during normal breathing.
3. *Contrast injection during the VM*: the mixed solution was injected 5 s after the patient was asked to begin 'pushing'; the sequence was repeated if the number of microembolic signals (MES) was low/absent.

Any MES recorded 5–12 s after the injection were considered indicative of an RLS at the atrial level; if they occurred later, a pulmonary atrium-ventricular fistula was suspected.

For the quantitative assessment of the amount of RLS, we followed the classification proposed by Serena et al. (12): small (less than 10 microbubbles) and large (10 microbubbles or more) shunts with further subdivision of large shunts in 'shower' (more than 25 microbubbles) and 'curtain' (uncountable signals) patterns.

### Statistical analysis

TEE served as the reference standard (13). Sensitivity was determined as the percentage of true-positive findings (RLS by both methods) compared with true-positive plus false-negative findings (ce-TCD negatives but TEE positives). Specificity was calculated as the percentage of true-negative findings (no RLS by both methods) compared with true-negative plus false-positive findings (ce-TCD positives but TEE negatives).

The positive predictive value was determined as the percentage of true-positive findings compared with true- plus false-positive findings. The negative predictive value was determined as the percentage of true-negative findings compared with true- plus false-negative findings. Diagnostic accuracy was calculated as the percentage of true-positive plus true-negative findings compared with the total number of patients examined.

## Results

From November 1997 to December 2006, 86 patients with a previous transient ischemic attack (TIA), or stroke, and a PFO have been submitted to transcatheter closure. All had a complete neurological and cardiological assessment: history and physical evaluation, computed tomography or magnetic resonance study of the brain and intracranial arteries, echo-Doppler investigation of the carotid and vertebral arteries, electrocardiogram, transthoracic, and TEE. Patients with coagulation abnormalities, vasculitis, atrial fibrillation, mitral valve disease, marked left ventricular dilatation or aneurysm, and soft atheromas of the aorta were excluded.

We recommended percutaneous closure of the PFO if a patient fulfilled any of the following conditions: (i) age less than 55 years; (ii) a 'large' RLS (spontaneous, or more than 20 microbubbles upon valsalva, as detected by a ce-TCD examination), or presence of an ASA; (iii) anticoagulant therapy was unsuitable or had already failed; (iv) more than one stroke/TIA had already occurred (1, 14). After the procedure, prophylaxis against bacterial endocarditis and antiplatelet therapy was recommended for 6 months.

Regular follow-up was provided at 3, 6, and 12 months and yearly thereafter. All patients were invited to have a TEE within 6 months; 10 refused. Of the remaining 76, 5 declined to have the ce-TCD. Of the 71 subjects in whom the ce-TCD was attempted, no signal could be obtained from either MCA owing to poor acoustic windows in 3 (4.2%), thus leaving 68 patients with both the TEE and ce-TCD studies. All patients signed a consent form for the procedures. The study received the approval from the local ethical committee.

A total of 38 men and 30 women were studied. Their mean age was 49 ± 13 years: 45 (66%) were less than 55 years old. Thirty-four patients had suffered a stroke and 34 a TIA. More than one event had occurred in 16 (23.5%). Migraine with aura was present in seven cases (10%).

Computed tomography or magnetic resonance imaging confirmed a cerebral ischemic lesion in 65 (95%). Risk factors for cerebrovascular diseases were: hypercholesterolemia in 25 (37%), hypertension in 21 (31%), current cigarette smoking in 16 (26%), and diabetes in 2 (3%). The investigations were well tolerated by all the subjects without side effects.

As shown in Table 1, following the classification based on the TEE criteria, only six patients had a large (more than 20 microbubbles) residual RLS. The result was moderately positive (11–20 microbubbles) in two. The shunt was absent or non-significant (0–10 microbubbles) in 60.

By ce-TCD, no RLS or a small one (less than 10 microbubbles) was detected in 37 (54.4%) of the 68 patients. The RLS was large in 10 (14.7%) patients; 12 (17.7%) had a curtain pattern and 9 (13.2%) a shower pattern.

The eight strongly and moderately positive TEE results were correctly identified by either a curtain or a shower pattern at ce-TCD. However, among the 60 TEE studies with absent or non-significant findings (0–10 microbubbles), there were six shower and seven curtain patterns.

However, all of the 47 cases with less than 25 microbubbles were identified by ce-TCD as either closed or with a non-significant RLS at TEE. However, of the 21 shower and curtain patterns identified by ce-TCD, 13 were recorded by TEE as showing no or non-significant RLS.

We then compared the aforementioned findings in a dichotomic way: the TEE was classified as positive when the RLS was large (more than 20 microbubbles) and the ce-TCD results were considered positive only when a shower or curtain pattern was observed (Table 2).

Assuming TEE as the gold standard, the sensitivity was 100% (confidence interval: 60.9–100%); the specificity was 75.8% (confidence interval: 63.9–84.8%); the positive predictive value was 28.5%; the negative predictive value was 100%; and the diagnostic accuracy was 77.9%.

**Table 1** Cross table of the classification of 68 patients by transesophageal echocardiography (TEE) and contrast-enhanced transcranial Doppler (ce-TCD; mb indicates the number of microbubbles)

| | TEE | | | |
|---|---|---|---|---|
| | >20 mb | 11–20 mb | 0–10 mb | Total |
| ce-TCD | | | | |
| Curtain | 5 | | 7 | 12 |
| Shower | 1 | 2 | 6 | 9 |
| 10–25 mb | | | 10 | 10 |
| 0–10 mb | | | 37 | 37 |
| Total | 6 | 2 | 60 | 68 |

**Table 2** Contingency table of the classification of the patients as having a residual right-to-left shunt (RLS; positive) and without a residual RLS (negative). Transesophageal echocardiography (TEE) is considered as the gold standard

| | TEE | | |
|---|---|---|---|
| | Positive | Negative | Total |
| ce-TCD | | | |
| Positive | 6 | 15 | 21 |
| Negative | 0 | 47 | 47 |
| Total | 6 | 62 | 68 |

## Discussion

Percutaneous transcatheter closure of the foramen ovale is being increasingly employed as a way of preventing recurrences of stroke of undetermined cause, although proof is lacking of its superiority compared with anticoagulant or antiaggregant therapy (15, 16). The rationale of this solution resides in the abolition of any RLS across the IAS, as the postulated mechanism is that of a paradoxical embolism (17). However, this goal is not always achieved.

In a consecutive series of 68 patients following transcatheter closure of PFO, we found that ce-TCD revealed a higher number of patients with a residual RLS compared with TEE. A curtain or shower pattern was recorded in 21 (30.9%): of these 12 patients, only 6 were classified as large by TEE. The percentage of patients with residual RLS of any size that was found by TEE (22/68; 32%) was similar to the 27% reported by Windecker (4).

A residual shunt by TEE has been reported to range from 0% (18, 19) to 49% (20), with most of the other studies varying between 2% and 34% (4, 5, 11, 21–26). However, these results cannot be

meaningfully compared because of the different methods and criteria adopted, as gleaned from a brief review of the pertinent literature. No criteria of RLS were given in three papers (4, 18, 24); color Doppler was used in two (21, 23); echocontrast in seven, of which: three (11, 19, 22) adopted a three-grade scale (0, 3–20, >20 microbubbles); four adopted Websters's (27) four-grade classification (5, 26) or a variant of it (20). Finally, Schwerzmann (25) employed Schuchlenz's (28) descriptive assessment (minimal, cloud, and intense).

Anzola et al. (9) reported 8% of residual shunt by ce-TCD at 6 months, whereas Spencer et al. (29) found 34% of incomplete closure, as measured by power M-mode ce-TCD.

According to the report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (7), ce-TCD is comparable with contrast TEE for detecting RLS as a result of PFO. Belvis et al. (8) have reported almost perfect concordance between the twotechniques. Recently, other researchers demonstrated a statistical correlation between the results obtained by the two techniques, with reliable concordance (30–32).

Anzola (9) has suggested that ce-TCD is superior to TEE in the detection of residual RLS, even though this suggestion is still debated (33). Residual shunt has been indicated in recurrent cerebrovascular accidents following percutaneous closure by Windecker et al. (4), and some authors have reported the implantation of a second device in such patients (34).

It is thus important not only to detect, but also to quantify a residual RLS. Anzola (9) has proposed that the number of microbubbles greater than 12 detected by ce-TCD at 3 months could be adopted as a cut-off value for prediction of failure. Schwerzmann et al. (25) have taken a 'more than minimal' residual shunt by TEE [i.e., a cloud of bubbles or intense opacification of the left atrium, as originally defined by Schuchlenz et al. (28)] as a reason for proposing the re-closure of the leaking PFO.

As recently confirmed by Zito et al. (30) and Kobayashi et al. (35), ce-TCD is a safe and low-cost investigation technique, which provides sensitivity and specificity comparable with ce-TEE. Our data showed that if ce-TCD is negative, then no further investigation is necessary, given the high sensitivity of ce-TCD. Our results are confirmatory of the ce-TCD performance in PFO detection. However, our study is specific of a selected population of patients who underwent PFO closure. In our clinical experience, we plan to use ce-TCD as a PFO-monitoring tool over time, recommending ce-TEE examination when in presence of a positive ce-TCD. Mangiafico et al. (31) underlined that ce-TCD and ce-TEE can be thought of as complementary. We agree that the two methodologies can provide complementary insights, as ce-TEE remains preferable in determining the size of residual RLS in patient follow-up.

In summary, we have found that ce-TCD is preferable to TEE to detect residual RLS after transcatheter closure of a PFO. The discomfort is much less, the VM can be performed with more reliability (14), and a suitable signal can almost always be obtained: our failure rate was 4.2%, compared with Serena et al.'s (13) 18.9%.

## Conclusions

ce-TCD appears to be the preferable technique to identify subjects with significant residual shunts after percutaneous closure of a PFO, also as a result of a lower discomfort to the subjects and the possibility of performing a better VM. Our data showed that, in patient follow-up, if ce-TCD is negative, no further examination may be necessary; if ce-TCD shows a residual shunt, it is advisable to perform a TEE investigation.

## References


1. Landzberg MJ, Khairy P. Indications for the closure of patent foramen ovale. Heart 2004;**90**:219–24.
2. Anzola GP, Frisoni GB, Morandi E, Casilli F, Onorato E. Shunt-associated migraine responds favorably to atrial septal repair: a case-control study. Stroke 2006;**37**: 430–4.
3. Walsh KP, Wilmshurst PT, Morrison WL. Transcatheter closure of patent foramen ovale using the Amplatzer septal occluder to prevent recurrence of neurological decompression illness in divers. Heart 1999;**81**:257–61.
4. Windecker S, Wahl A, Chatterjee T et al. Percutaneous closure of patent foramen ovale in patients with paradoxical embolism: long-term risk of recurrent thromboembolic events. Circulation 2000;**101**:893–8.
5. Wahl A, Meier B, Haxel B et al. Prognosis after percutaneous closure of patent foramen ovale for paradoxical embolism. Neurology 2001;**57**:1330–2.
6. Wahl A, Windecker S, Meier B. Evaluation and treatment of abnormalities of the interatrial septum. Catheter Cardiovasc Interv 2004;**63**:94–103.
7. Sloan MA, Alexandrov AV, Tegeler CH et al. Assessment: transcranial Doppler ultrasonography: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2004;**62**:1468–81.
8. Belvis R, Leta RG, Marti-Fabregas J et al. Almost perfect concordance between simultaneous transcranial Doppler and transesophageal echocardiography in the quantification of right-to-left shunts. J Neuroimaging 2006;**16**:133–8.
9. Anzola GP, Morandi E, Casilli F, Onorato E. Does transcatheter closure of patent foramen ovale really "shut the door?" A prospective study with transcranial Doppler. Stroke 2004;**35**:2140–4.

10. Pearson AC, Nagelhout D, Castello R, Gomez CR, Labovitz AJ. Atrial septal aneurysm and stroke: a transesophageal echocardiographic study. J Am Coll Cardiol 1991;**18**:1223–9.
11. Spies C, Strasheim R, Timmermanns I, Schraeder R. Patent foramen ovale closure in patients with cryptogenic thrombo-embolic events using the cardia PFO occluder. Eur Heart J 2006;**27**:365–71.
12. Serena J, Segura T, Perez-Ayuso MJ, Bassaganyas J, Molins A, Davalos A. The need to quantify right-to-left shunt in acute ischemic stroke: a case-control study. Stroke 1998;**29**:1322–8.
13. Droste DW, Kriete JU, Stypmann J et al. Contrast transcranial Doppler ultrasound in the detection of right-to-left shunts: comparison of different procedures and different contrast agents. Stroke 1999;**30**:1827–32.
14. Lock JE. Patent foramen ovale is indicted, but the case hasn't gone to trial. Circulation 2000;**101**:838.
15. Messe SR, Silverman IE, Kizer JR et al. Practice parameter: recurrent stroke with patent foramen ovale and atrial septal aneurysm: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2004;**62**:1042–50.
16. Sacco RL, Adams R, Albers G et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. Circulation 2006;**113**:e409–49.
17. Lechat P, Mas JL, Lascault G et al. Prevalence of patent foramen ovale in patients with stroke. N Engl J Med 1988;**318**:1148–52.
18. Butera G, Bini MR, Chessa M, Bedogni F, Onofri M, Carminati M. Transcatheter closure of patent foramen ovale in patients with cryptogenic stroke. Ital Heart J 2001; **2**:115–8.
19. Du ZD, Cao QL, Joseph A et al. Transcatheter closure of patent foramen ovale in patients with paradoxical embolism: intermediate-term risk of recurrent neurological events. Catheter Cardiovasc Interv 2002;**55**:189–94.
20. Martin F, Sanchez PL, Doherty E et al. Percutaneous transcatheter closure of patent foramen ovale in patients with paradoxical embolism. Circulation 2002;**106**:1121–6.
21. Hung J, Landzberg MJ, Jenkins KJ et al. Closure of patent foramen ovale for paradoxical emboli: intermediate-term risk of recurrent neurological events following transcatheter device placement. J Am Coll Cardiol 2000;**35**:1311–6.
22. Braun MU, Fassbender D, Schoen SP et al. Transcatheter closure of patent foramen ovale in patients with cerebral ischemia. J Am Coll Cardiol 2002;**39**:2019–25.
23. Onorato E, Melzi G, Casilli F et al. Patent foramen ovale with paradoxical embolism: mid-term results of transcatheter closure in 256 patients. J Interv Cardiol 2003;**16**: 43–50.
24. Hong TE, Thaler D, Brorson J, Heitschmidt M, Hijazi ZM. Transcatheter closure of patent foramen ovale associated with paradoxical embolism using the amplatzer PFO occluder: initial and intermediate-term results of the U.S. multicenter clinical trial. Catheter Cardiovasc Interv 2003;**60**:524–8.
25. Schwerzmann M, Windecker S, Wahl A et al. Percutaneous closure of patent foramen ovale: impact of device design on safety and efficacy. Heart 2004;**90**:186–90.
26. Windecker S, Wahl A, Nedeltchev K et al. Comparison of medical treatment with percutaneous closure of patent foramen ovale in patients with cryptogenic stroke. J Am Coll Cardiol 2004;**44**:750–8.
27. Webster MW, Chancellor AM, Smith HJ et al. Patent foramen ovale in young stroke patients. Lancet 1988;**2**: 11–2.
28. Schuchlenz HW, Weihs W, Horner S, Quehenberger F. The association between the diameter of a patent foramen ovale and the risk of embolic cerebrovascular events. Am J Med 2000;**109**:456–62.
29. Spencer MP, Moehring MA, Jesurum J, Gray WA, Olsen JV, Reisman M. Power m-mode transcranial Doppler for diagnosis of patent foramen ovale and assessing transcatheter closure. J Neuroimaging 2004;**14**:342–9.
30. Zito C, Dattilo G, Oreto G et al. Patent foramen ovale: comparison among diagnostic strategies in cryptogenic stroke. Echocardiography 2009;**26**:495–503.
31. Mangiafico S, Scandura S, Ussia GP et al. Transesophageal echocardiography and transcranial color Doppler: independent or complementary diagnostic tests for cardiologists in the detection of patent foramen ovale? J Cardiovasc Med 2009;**10**:143–8.
32. Telman G, Yalonetsky S, Kouperberg E et al. Size of PFO and amount of microembolic signals in patients with ischemic stroke or TIA. Eur J Neurol 2008;**15**: 969–72.
33. Schuchlenz HW. Contrast ultrasound techniques in the detection and quantification of patent foramen ovale: myth versus reality. Stroke 2004;**35**:2755; author reply, 6.
34. Schwerzmann M, Windecker S, Wahl A et al. Implantation of a second closure device in patients with residual shunt after percutaneous closure of patent foramen ovale. Catheter Cardiovasc Interv 2004;**63**:490–5.
35. Kobayashi K, Igushi Y, Kimura K et al. Contrast transcranial Doppler can diagnose large patent foramen ovale. Cerebrovasc Dis 2009;**27**:230–4.