Sensitivity of contrast-enhanced transthoracic echocardiography for the detection of residual shunts after percutaneous patent foramen ovale closure

Hongling Zhao, MD\textsuperscript{a}, Qingxiong Yue, MD\textsuperscript{b}, Tao Wang, PhD, MD\textsuperscript{c}, Lin Wang, MD\textsuperscript{c}, Zhanqi Pang, MD\textsuperscript{c}, He Dong, MD\textsuperscript{c}, Jian Yang, MD\textsuperscript{c}, Yawen Li, MD\textsuperscript{c}, Shijun Li, MD\textsuperscript{c,∗}

Abstract
The objective of this study is to investigate the sensitivity of contrast-enhanced transthoracic echocardiography (c-TTE) versus transesophageal echocardiography (TEE) to detect a residual right-to-left shunt (RLS) following a transcatheter patent foramen ovale (PFO) closure. A self-controlled study was conducted in a tertiary referral hospital. 57 patients with PFO who had experienced migraines underwent percutaneous PFO closure. c-TTE, TEE, and contrast-enhanced transcranial Doppler (c-TCD) at resting and Valsalva maneuver were performed during the 3-month follow-up after the closure. The closure devices were successfully implanted in all patients without complications. Three months after closure, TEE did not detect residual Valsalva shunts in any of the 57 patients; residual valsealva shunts were found via c-TTE in 15 of the 57 patients and were also observed via c-TCD. When c-TTE and/or c-TCD were used, the rate of residual RLSs detected in patients who underwent PFO closure was 26.32%, which was significantly different than the rate detected using TEE ($P < .05$). c-TTE and c-TCD showed equivalent sensitivity in evaluating transcatheter closure of a PFO. c-TTE could be a more cost-effective and reliable method to detect the residual shunt after PFO closure.

Abbreviations: CDFI = color Doppler flow imaging, c-TCD = contrast-enhanced transcranial Doppler, c-TTE = contrast-enhanced transthoracic echocardiography, PFO = patent foramen ovale, RLS = right-to-left shunt, TEE = transesophageal echocardiography.

Keywords: contrast transcranial Doppler, patent foramen ovale, percutaneous closure, residual shunt, transesophageal echocardiography, transthoracic echocardiography

1. Introduction
A patent foramen ovale (PFO) is an intra-atrial latent conduit located between the septum primum and septum secundum that opens when the pressure of the right atrium exceeds the pressure of left atrium and leads to a right-to-left shunt (RLS). A patent foramen ovale is a common condition that occurs in up to 25% of the general population.\textsuperscript{[1]} An RLS caused by PFO has been implicated in the pathogenesis of migraine headaches. Some chemicals that are cleared by the lungs are shunted via a PFO and induce migraine symptoms in susceptible individuals; closure of the PFO will ameliorate or eliminate headache. Subjects with migraine could benefit from percutaneous closure of their PFO.\textsuperscript{[2,3]}

Ultrasoundography is the major method for the diagnosis of a PFO. Many studies have investigated the sensitivity of contrast-enhanced transthoracic echocardiography (c-TTE), contrast-enhanced transcranial Doppler (c-TCD), and transesophageal echocardiography (TEE) on the screening, diagnosis, and quantification of PFOs. TEE, which can show the atrial septal anatomy and an RLS, is considered to be the gold standard for the diagnosis of a PFO.\textsuperscript{[4]} However, TEE is a semi-invasive method that increases the discomfort of patients. c-TTE is a highly sensitive method to detect an RLS. c-TCD is also a highly sensitive method to detect an RLS and c-TCD without observing anatomy. Few studies have mentioned the sensitivity of the different ultrasonographic methods in detecting residual shunts after transcatheter closure. Therefore, the goal of this study is to investigate the sensitivity of TEE, c-TTE, and c-TCD for detecting a residual RLS following a transcatheter closure for migraine headaches, and we expect to determine the most suitable method for follow-up after a transcatheter closure.

2. Methods
2.1. Study population
Around 57 patients with PFO who experienced migraines were enrolled in this study from June 2012 to July 2016. They undergo cranio-cerebral CT or MRI in order to exclude a local cause for
headaches. Subjects were excluded from the study if they had a history of seizure disorder or other organic central nervous system disease, headaches other than migraines, or evidence of alcohol or substance abuse within the previous year. Furthermore, subjects were ineligible for transcatheter closure if they had a history of intracardiac thrombus or tumor, acute or recent (within 6 months) myocardial infarction or unstable angina, left ventricular aneurysm, atrial fibrillation.

The baseline characteristics of patients are summarized in Table 1. The closure device was implanted with a Cardi-O-Fix PFO Occluder (Starway medical, Shenzhen, China). All the patients who underwent PFO closure received dual antiplatelet therapy (100 mg of aspirin plus 75 mg of clopidogrel per day) for 3 months, followed by single antiplatelet therapy for 6 months. This study was approved by the Ethics Committee of Dalian Municipal Central Hospital. Written informed consent was obtained from each patient. All patients underwent TEE with color Doppler flow imaging (CDFI), c-TTE and c-TCD performed by 3 different technicians before and 3 months after the closure procedure. The ultrasound technicians were blind to the subjects’ groups and the results of the parallel ultrasound that was performed by the other technician.

2.2. Agitated saline contrast test

A mixture of 9 mL of saline and 1 mL of air was agitated using 2 syringes connected to a 3-way stopcock to make the air–saline mix. The bolus of saline mixture was injected into the antecubital vein within 2–3 minutes.

Ultrasound (SSH-880CV (Aplio Artida), Toshiba, Japan) Criteria

Using c-TTE, the shunt was determined to be Grade I (no microembolic signal), Grade II (small; 1–10 microembolic signals), Grade III (medium; 10–20 microembolic signals), or Grade IV (large; >20 microembolic signals (Fig. 1))

TCD (EMS-9E, Delica, China) 2-MHz probe

Using c-TCD, the shunt was determined to be Grade I (no microembolic signal), Grade II (small; 1–10 microembolic signals), Grade III (medium; >10 microembolic signals), or Grade IV (large; >10 microembolic signals with “curtain”) (Fig. 1)

2.3. Statistical analysis

All data for continuous variables are reported as the mean ± standard deviation or the median. A chi-square test was used to

Table 1
Baseline characteristics of patients with patent foramen ovale.

|                   | n  | %      |
|-------------------|----|--------|
| Average age       | 48.5 ± 4.7 |
| Sex               |    |        |
| Male              | 24 | 42.11% |
| Female            | 33 | 57.89% |
| Cryptogenic stroke with migraine | 9  | 15.79% |
| Atrial septal aneurysm | 15 | 26.32% |
| TCD shunt grade before closure |    |        |
| Resting I         | 15 | 26.32% |
| II                | 9  | 15.79% |
| III               | 12 | 21.05% |
| IV                | 21 | 36.84% |
| Valsalva I        | 0  | 0.00%  |
| II                | 9  | 15.79% |
| III               | 9  | 15.79% |
| IV                | 39 | 68.42% |
| PFO diameter under TEE, mm | 1–4 | |
| Size of closure device |    |        |
| 18/25 mm          | 51 | 89.50% |
| 18/18 mm          | 3  | 5.25%  |
| 30/30 mm          | 3  | 5.25%  |

PFO = patent foramen ovale; TCD = transcranial Doppler, TEE = transeophageal echocardiography.

Figure 1. Shunt in c-TTE and c-TCD: The shunt was defined as Grade I [no microembolic signal c-TCD (Aa) and c-TTE (1Ab)], Grade II (small; 1–10 microembolic signals c-TCD (Bb) and c-TTE (Fig. Bb), Grade III (medium; >10 microembolic signals), or Grade IV (large; >10 microembolic signals with "curtain" c-TCD (Ca) and c-TTE (Cb)].
compare categorical variables between groups. A Student’s test or a Wilcoxon rank-sum test was used to compare continuous variables between groups. A value of $P < .05$ was considered to be statistically significant. All analyses were performed using SPSS software version 11.0 (SPSS, Chicago, IL).

3. Results

3.1. Patients’ characteristics

Around 57 consecutive patients (24 males, 33 females; 48.5 ± 4.7 years) were diagnosed PFO. Among 57 patients, 9 patients suffered both migraine headache and cryptogenic stroke (an ischemic within the previous 6 months with no identifiable cause other than a PFO), and 15 patients were concomitant atrial septal aneurysm. All the patients underwent percutaneous PFO closure for successful implantation of closure device without any complications (Table 1).

The sensitivity of different ultrasonographic methods to detect residual RLS after percutaneous PFO closure

Three months after undergoing a closure, patients were examined via transthoracic echocardiography with CDFI, TEE with CDFI, c-TCD and c-TTE. TEE with CDFI showed the closure device in the correct position without any signs of a residual shunt at rest or during a Valsalva maneuver. TEE with CDFI did not show any signals crossing the atrial septum or residual right-to-left shunt. The current study showed that TEE with CDFI did not detect any residual Valsalva shunts in the 57 patients; c-TTE detected residual Valsalva shunts in 15 of the 57 patients, which were also detected by c-TCD. There was a significant difference in residual Valsalva shunt detection by c-TTE or c-TCD compared to detection by TEE ($P < .05$). Two different technicians performed the c-TTE and c-TCD were kept blind to the results of the parallel ultrasound that was performed by the other technician, and the 2 observers achieved the same result for each method. Thus, there is no inter-observer or intraobserver variability for detecting residual shunt by each method.

4. Discussion

The current study showed that TEE with CDFI did not detect residual shunts in any of the 57 patients evaluated 3 months after closure, and residual shunts were detected in 15 of the 57 patients by either c-TTE or c-TCD. c-TTE and c-TCD showed equivalent sensitivity in evaluating transcatheter closure of a PFO.

Percutaneous PFO closure is a safe and effective procedure that can treat migraine headaches. However, the initial transcatheter closure still does not completely eliminate the right-to-left shunt. A residual RLS is not uncommon soon after a closure procedure, and approximately 19.5% and 18.2% of patients present with residual shunts 6 months and 12 months after closure, respectively. However, most of these residual shunts are small, with <3% being persistent large shunts 1 year after closure. Persistent moderate-to-severe residual shunts after closure may increase the recurrence of migraine headaches. Therefore, follow-up after a closure to detect residual shunts is of vital importance. More residual shunt can be detected at 3 months after the closure procedure, thus, we chose to perform ultrasonography at 3 months after the closure procedure in order to find the most sensitive method.

Ultrasonography, including TEE, c-TTE and c-TCD, is the main method to diagnose and evaluate a PFO before and after closure. These methods have been used in different studies to evaluate residual shunts. A multicentric survey showed that 42.4% to 75% of patients who underwent a closure were evaluated by c-TTE alone, 6.5% to 23.4% of patients were fellow up with c-TCD alone or TEE alone. TEE and c-TTE are used in...
prospective, randomized, double-blinded, controlled studies to evaluate PFO, such as the RESPECT Trial,[10] CLOSE Trial,[11] and PRIMA Trial.[12] Studies have shown that different ultrasonographic methods have differing sensitivities in evaluating an RLS of PFO.[13] A systematic review and diagnostic test accuracy meta-analysis shows that c-TCD is more sensitive than TTE in the detection of PFO in patients with cryptogenic cerebral ischemia. The overall diagnostic yield of c-TCD appears to outweigh that of c-TTE.[13] The use of c-TTE and c-TCD to detect residual shunts after percutaneous PFO closure may be more sensitive and comfortable than TEE. Our study may be helpful in the follow-up evaluations after the PFO closure.

There are several limitations in our study. First, the patient number is relative small in current study. Second, we only detect residual shunts by the 3 ultrasonographic methods and cardiac nuclear magnetic resonance (CMR) may be better method to detect residual shunts, but CMR was expensive and could not be performed for 3 months after PFO closure. Third, a receiver operating characteristic curve and calculating the area under the curve under the receiver operating characteristic curve maybe helpful to evaluate the 3 ultrasonography methods detecting the residual shunts after percutaneous PFO closure. It is hard to make a receiver operating characteristic curve because of lacking of a golden standard, such as cardiac nuclear magnetic resonance. Only little of our patient performed TEE with agitated saline or contrast agents, and we thought it has more dif fi

In conclusion, this study showed c-TTE and c-TCD show equivalent sensitivity in evaluating transcatheter closure of a PFO. c-TTE could be a more cost-effective and reliable method to detect the residual shunt after PFO closure.

Author contributions

Investigation: Qingxiong Yue, Jian Yang.
Methodology: Qingxiong Yue, Lin Wang, Zhan-qi Pang, He Dong, Ya-wen Li.
Project administration: Shijun Li.

References

[1] Jonathan MT, Babak A. Does patent foramen ovale promote cryptogenic stroke and migraine headache? Tex Heart Inst J 2005;32:362–5.
[2] Butera G, Biondi-Zoccai GG, Carminati M, et al. Systematic review and meta-analysis of currently available clinical evidence on migraine and patent foramen ovale percutaneous closure: much ado about nothing? Catheter Cardiovasc Interv 2010;75:494–504.
[3] Martle HP, Evers S, Hildick-Smith D, et al. Percutaneous closure of patent foramen ovale in migraine with aura, a randomized controlled trial. Eur Heart J 2016;37:2029–36.
[4] Schneider B, Zienkiewicz T, Jansen V, et al. Diagnosis of patent foramen ovale by transesophageal echocardiography and correlation with autopsy findings. Am J Cardiol 1996;77:1202–9.
[5] Alameidine F, Block PC. Transcatheter patent foramen ovale closure for secondary prevention of paradoxical embolic events: acute results from the FORECAST registry. Catheter Cardiovasc Interv 2004;62:512–6.
[6] Trabattoni D, Fabbriocchi F, Montorsi P, et al. Sustained long-term benefit of patent foramen ovale closure on migraine. Catheter Cardiovasc Interv 2011;77:570–4.
[7] Caputi L, Butera G, Anzola GP, et al. Italian Patent Foramen Ovale Survey investigators. Residual shunt after patent foramen ovale closure: preliminary results from Italian patent foramen ovale survey. J Stroke Cerebrovasc Dis 2013;22:e219–26.
[8] Van H, Poommipanit P, Shalaby M, et al. Sensitivity of transcranial Doppler versus intracardiac echocardiography in the detection of right-to-left shunt. JACC Cardiovasc Imaging 2010;3:343–8.
[9] Snijder RJ, Post MC2, Mulder TB, et al. Persistent high residual shunt rate 2 years after patent foramen ovale closure using a bioabsorbable device. JACC Cardiovasc Interv 2014;7:106–7.
[10] Carroll JD, Saver JL, Thaler DE, et al. RESPECT Investigators. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. N Engl J Med 2013;368:1092–100.
[11] Mas JL, Derumeaux G, Guillou B, et al. CLOSE investigators. Patent foramen ovale closure or anticoagulation vs antiplatelets after stroke. N Engl J Med 2017;377:1011–21.
[12] Tobis JM, Charles A, Silberstein SD, et al. Percutaneous closure of patent foramen ovale in patients with migraine: the PREMIUM trial. J Am Coll Cardiol 2017;70:2766–74.
[13] Katsanos AH, Psaltopoulou T, Sergentanis TN, et al. Transcranial Doppler versus transthoracic echocardiography for the detection of patent foramen ovale in patients with cryptogenic cerebral ischemia: a systematic review and diagnostic test accuracy meta-analysis. Ann Neurol 2016;79:625–35.