Original Article

Diagnostic value of contrast-enhanced ultrasonography for patent foramen ovale detection

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Background: Patent foramen ovale (PFO) has been associated with migraine, cryptogenic stroke (CS), and hypoxemia. However, which examination method is most reliable remains controversial. This study sought to investigate the diagnostic value of contrast-enhanced ultrasonography (cU), including contrast-enhanced transcranial Doppler (cTCD), contrast transthoracic echocardiography (cTTE), and contrast transesophageal echocardiography (cTEE), for PFO; and to determine the best diagnostic strategy.

Methods: This retrospective observational study included a total of 147 consecutive patients suspected PFO at The First Hospital of Shanxi Medical University between October 2019 and January 2022. The patients also underwent cTCD, cTTE, and cTEE examinations. The standard for the diagnosis of PFO was confirmation of the presence of PFO by color Doppler flow signals or contrast microbubbles (MBs) passing through the foramen ovale.

Results: A total of 123 patients were diagnosed with PFO and 24 patients without PFO during the study period. The detectable rates of cTCD, cTTE, and cTEE were 120 (97.56%), 110 (89.43%), and 121 (98.37%), respectively. The sensitivity between cTCD and cTEE for PFO were comparable [97.56%, 95% confidence interval (CI): 92.5% to 99.4% *vs.* 98.37%, 95% CI: 93.7% to 99.7%; P>0.99], and the sensitivity of both were higher than that of cTTE (89.43%, 95% CI: 82.3% to 94.0%; P=0.02 and P=0.001, respectively). In addition, the specificity of cTEE for PFO was significantly higher than that of cTCD (100%, 95% CI: 82.3% to 100.0% *vs.* 75.00%, 95% CI: 53.0% to 89.4%; P<0.001) and cTTE (100%, 95% CI: 82.3% to 100.0% *vs.* 75.00%, 95% CI: 53.0% to 89.4%; P<0.001). Further, the semi-quantitative classification ability of cTCD for PFO with right-to-left shunt (RLS) was significantly higher than that of cTTE and cTEE (P=0.02 and P<0.001, respectively), and that of cTTE was significantly higher than that of cTEE (P=0.01). The Spearman analysis showed that the degree of RLS was positively correlated with the inner diameter of the PFO (r=0.695, P<0.001).

Conclusions: The combination of cTCD and cTEE may provide a favorable strategy for the diagnosis of PFO.

Keywords: Ultrasonography; patent foramen ovale (PFO); diagnosis; semi-quantitative classification ability; right-to-left shunt (RLS)

Submitted Feb 28, 2024. Accepted for publication Apr 26, 2024. Published online May 21, 2024.
doi: 10.21037/jtd-24-330
View this article at: https://dx.doi.org/10.21037/jtd-24-330

Introduction

Patent foramen ovale (PFO) is part of a group of entities known as atrial septal defects and is a remnant of normal fetal anatomy (1). The foramen ovale is an embryonic defect in the interatrial septum that allows the passage of oxygenated blood from the right atrium to the left atrium. In most people, the septum primum and septum secundum become tight after birth and then adhere and fuse to each other to gradually form a permanent atrial septum. If fusion is not complete by the age of 3 years or older, a cleft-like channel is left behind, which is referred to as a PFO. It has been reported that the prevalence of PFO in adults is approximately 25% (1,2). Recently, a growing number of studies (3,4) have shown that patients with PFO who have right-to-left shunt (RLS; PFO-RLS) are at higher risk of cryptogenic stroke (CS), migraine, transient ischemic attack (TIA), and decompression sickness than the general population.

PFO is of clinical significance because it may be a source of thrombus formation or serve as a conduit for paradoxical embolism (4,5). Recent randomised clinical trials showed that the efficacy of PFO closure in preventing cerebral stroke recurrence is higher than that of drug therapy (6-8). Recent clinical investigations have confirmed the beneficial effects of the percutaneous device closure of PFO, and the anatomical features of PFO and the adjacent atrial septum have become key components for shared decision making in choosing the optimal management strategy for patients with CS and PFO (9-13).

The qualitative diagnosis and quantitative analysis of PFO-RLS is a key process in the interventional treatment of PFO occlusion; therefore, the accurate diagnosis of PFO and the quantitative diagnosis of PFO-RLS are of great importance. Right heart catheterisation with demonstration of a guidewire crossing the septum is the most accurate method to confirm the presence of PFO; but it is not suitable as a preliminary examination because it is invasive. Currently, various methods, including contrast-enhanced transcranial Doppler (cTCD), contrast transthoracic echocardiography (cTTE), and contrast transesophageal echocardiography (cTEE) have been used for the diagnosis of PFO-RLS.

Various studies have investigated the diagnostic values of cTCD, cTTE, and cTEE for PFO-RLS (14-16). Each method has its advantages and disadvantages. cTCD is a non-invasive method of detecting RLS that does not rely on tomography. Studies have shown that cTCD has the highest sensitivity of the three. It is also the least expensive, but it does not provide any information on septal anatomy and related structures (17,18). cTTE is non-invasive and intuitive, but the image quality is affected by gas, obesity and Valsalva movement; and the size of the PFO cannot be determined (19). cTEE is considered the gold standard for the diagnosis of PFO. It can directly observe the anatomical structure of FPO and the origin of microbubbles (MBs)

Highlight box

Key findings

- The findings of this study showed that contrast-enhanced transcranial Doppler (cTCD) had a higher sensitivity and semi-quantitative classification capability than contrast transthoracic echocardiography (cTTE) for the diagnosis of patent foramen ovale (PFO) and has the potential to be a good screening method for PFO. Conversely, contrast transesophageal echocardiography (cTEE) had the highest specificity for diagnosing PFO, but its weakness is the invasiveness that limits it as a screening test.

What is known, and what is new?

- The presence of PFO is implicated in the pathogenesis of a number of medical conditions. Recent randomized clinical trials have shown evidence of the benefit of device closure compared with medical therapy in patients with cryptogenic stroke. The diagnosis of PFO and the quantitative analysis of right-to-left shunt (RLS) are required to decide treatment. Currently, various methods, including cTCD, cTTE, and cTEE, are used for the diagnosis of PFO-RLS. Most previous studies have only compared the diagnostic values of two methods, and very few studies have compared the diagnostic values of the three methods at the same time. In addition, debate continues as to the best diagnostic strategy.
- This study investigated the diagnostic value of contrast-enhanced ultrasonography, including cTCD, cTTE and cTEE, for PFO.

What is the implication, and what should change now?

- cTCD has the potential to be a first-line investigation examination for detecting RLS. The combination of cTCD and cTEE could provide a favorable strategy for the diagnosis of PFO and accessing RLS.

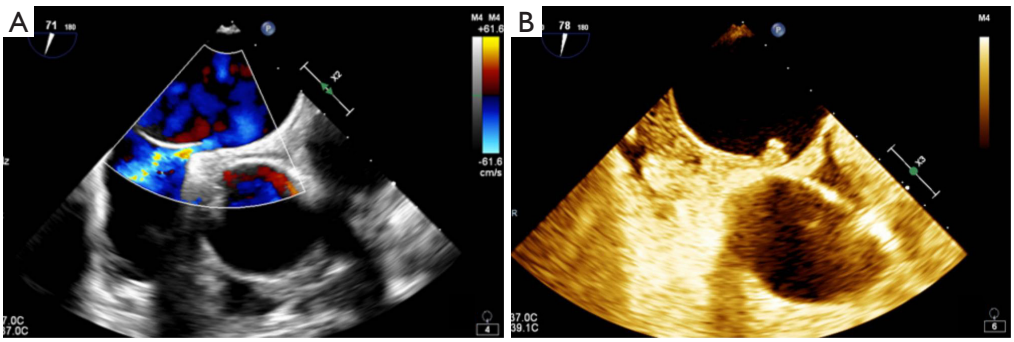

Figure 1 A 53-year-old male patient with PFO and migraine. (A) TEE showing the color Doppler signals of blood flow through the foramen ovale; (B) cTEE showing the crossing of MBs of contrast agent through the foramen ovale. PFO, patent foramen ovale; TEE, transesophageal echocardiography; cTEE, contrast transesophageal echocardiography; MB, microbubble.

in the left heart; however, it has the disadvantage of being semi-invasive, and it may be difficult to performed in stroke patients with dysphagia and/or poor cooperation (20,21). Most previous studies have only compared the diagnostic values of two methods (22-24), and the results of the studies are inconsistent. In the past, transesophageal echocardiography (TEE) was limited in the routine practices, and frequent use of sedation affected the results of TEE. Very few studies have compared the diagnostic values of the three methods at the same time. In addition, debate continues as to the best diagnostic strategy.

This study sought to investigate the diagnostic value of contrast-enhanced ultrasonography (cU), including cTCD, cTTE, and cTEE, for PFO, and to determine the best diagnostic strategy. We present this article in accordance with the STARD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-330/rc).

Methods

Study design and subjects

This retrospective observational study included a total of 147 consecutive patients suspected PFO at The First Hospital of Shanxi Medical University between October 2019 and January 2022. The patients also underwent cTCD, cTTE, and cTEE examinations. The standard for the diagnosis of PFO was confirmation of the presence of PFO by color Doppler flow signals or contrast MBs passing through the foramen ovale (17,19-21) (*Figure 1*). The exclusion criteria were as follows: (I) an undetectable temporal window; (II) concomitant extracranial and intracranial vascular stenosis, a brain tumor, or cerebral hemorrhage; (III) an inability to perform the Valsalva movement; (IV) pulmonary arteriovenous malformations on computed tomography or magnetic resonance imaging; (V) atrial septal defect, ventricular septal defect, patent ductus arteriosus and other congenital heart structural diseases.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of The First Hospital of Shanxi Medical University (No. 2021-k-k116). Informed consent was taken from all individual participants.

Data collection and definition

Details about the cTCD, cTTE, and cTEE examination procedures are provided in the supplementary materials (Appendix 1). The examination data were collected. In addition, clinical data, including age, sex, CS, migraine, dizziness, TIA, coronary heart disease, arrhythmia, the degree of shunting, PFO inner diameter, and PFO tunnel length, were collected. The PFO inner diameter was defined as the distance of no fusion between the primary and secondary septum of the atrial septum. The PFO tunnel length was defined as the degree of overlap between the primary and secondary septum of the atrial septum. The degree of PFO-RLS was measured by the semi-quantitative classification standard for the number of cTCD MBs and included: Grade 0, no microemboli and no RLS; Grade I, 1–10 microbubble (MB) signals, and mild RLS; Grade II, 11–25 MB signals, and moderate RLS; Grade III, >25 MB signals or rain curtains, and large RLS (22,25). The reference standard for the semi-quantitative classification of the number of MBs in the left heart of cTTE and cTEE

Table 1 Basic clinical data of PFO positive and PFO negative patients

Variables	PFO positive (n=123)	PFO negative (n=24)
Age (years), mean ± SD	43.45±15.14	44.29±15.78
Male/female (n)	58/65	9/15
CS (n)	56	10
Migraine (n)	48	9
Dizziness (n)	13	2
TIA (n)	4	1
Coronary heart disease (n)	1	2
Arrhythmia (n)	1	0

PFO, patent foramen ovale; SD, standard deviation; CS, cryptogenic stroke; TIA, transient ischemic attack.

Table 2 Comparison of findings of cTCD, cTTE and cTEE for the diagnosis of PFO (n)

Variables	PFO (+)	PFO (–)	Total
cTCD			
PFO (+)	120	6	126
PFO (–)	3	18	21
Total	123	24	147
cTTE			
PFO (+)	110	6	116
PFO (–)	13	18	31
Total	123	24	147
cTEE			
PFO (+)	121	0	121
PFO (–)	2	24	26
Total	123	24	147

cTCD diagnosis: sensitivity =97.56%, specificity =75%; cTTE diagnosis: sensitivity =89.43%, specificity =75%; cTEE diagnosis: sensitivity =98.37%, specificity =100%. cTCD, contrast-enhanced transcranial Doppler; cTTE, contrast transthoracic echocardiography; cTEE, contrast transesophageal echocardiography; PFO, patent foramen ovale.

was as follows: Grade 0: no MB in the left heart, and no RLS; Grade I: 1–10 MBs per frame in the left heart, and a small amount of RLS; Grade II: 11–30 MBs per frame in the left heart, and a medium amount of RLS; Grade III: >30 MBs per frame, or the left heart was almost filled with MBs, and a large amount of RLS (18,19).

Statistical analysis

SPSS Statistics version 26.0 was used to perform the statistical analysis. The continuous data are expressed as the mean ± standard deviation (SD) and were compared by the *t*-test. The categorical data are expressed as the number (percentage) and were compared by the Chi-square test. The Friedman rank-sum test was performed to examine the overall differences among the three measurements for the semi-quantitative grading of PFO-RLS. Spearman rank correlation was used to assess the correlations of the PFO-RLS degree with the inner diameter of the PFO and the length of the tunnel. A P value <0.05 was considered statistically significant.

Results

The general characteristics of the patients are shown in *Table 1*. A total of 123 patients were diagnosed with PFO and 24 patients without PFO. The detectable rates of cTCD, cTTE, and cTEE were 120 (97.56%), 110 (89.43%), and 121 (98.37%), with three (2.44%) false negatives and six (4.88%) false positives, 13 (10.57%) false negatives, and six (4.88%) false positives, and two (1.63%) false positives and no false negative, respectively (*Table 2*). The sensitivity of cTCD [97.56%, 95% confidence interval (CI): 92.5% to 99.4%] and cTEE (98.37%, 95% CI: 93.7% to 99.7%) for the diagnosis of PFO were of no statistical significance (P>0.99), and the sensitivity of both were significantly higher than that of cTTE (89.43%, 95% CI: 82.3% to 94.0%; P=0.02 and P=0.001, respectively). cTEE had a specificity of 100% (95% CI: 82.3% to 100.0%) for the diagnosis of PFO, which was significantly higher than those of cTCD (75.00%, 95% CI: 53.0% to 89.4%; P<0.001) and cTTE (75.00%, 95% CI: 53.0% to 89.4%; P<0.001) (*Table 2*).

The comparison of the semi-quantitative classification ability for PFO-RLS of the cTCD, cTTE, and cTEE by the Friedman rank-sum test revealed statistically significant differences among the three types of cUs (P<0.001). Further, the pair-wise comparison showed that the semi-quantitative classification ability for PFO-RLS of cTCD was significantly better than that of cTTE and cTEE (P=0.02 and P<0.001, respectively), and cTTE was significantly better than that of cTEE (P=0.01) (*Table 3* and

Table 3 Comparison of the semi-quantitative classification results of cTCD, cTTE, and cTEE for PFO-RLS (n)

Examination method	Grade 0 (none)	Grade I (low amount)	Grade II (moderate amount)	Grade III (high amount)	Z	P
cTCD	3	21	29	70	63.375	<0.001
cTTE	13	20	26	64		
cTEE	2	38	49	34		

cTCD, contrast-enhanced transcranial Doppler; cTTE, contrast transthoracic echocardiography; cTEE, contrast transesophageal echocardiography; PFO, patent foramen ovale; RLS, right-to-left shunt.

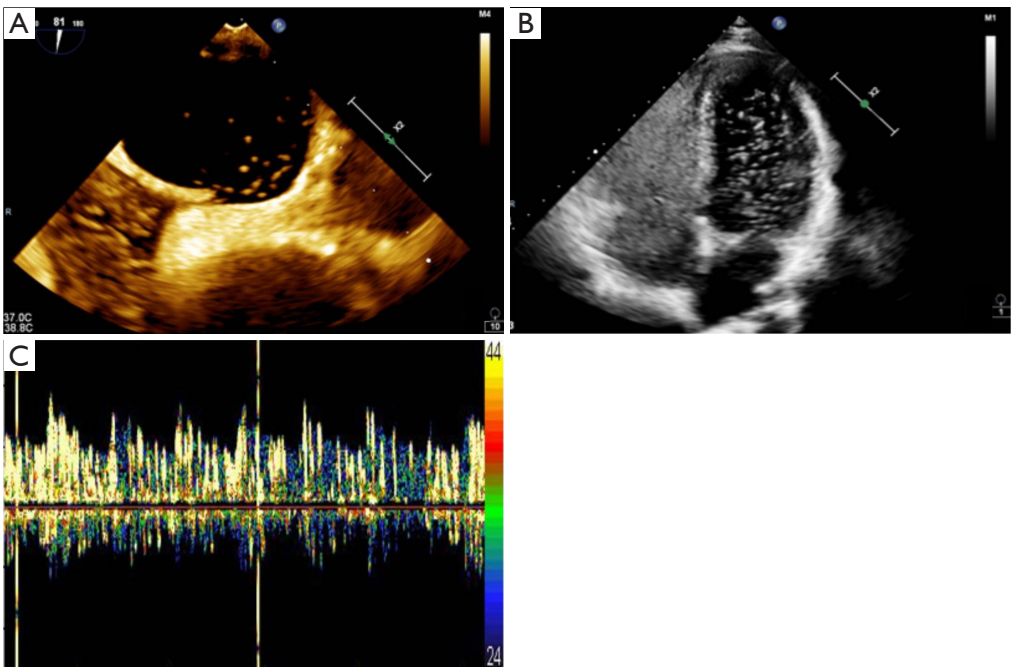

Figure 2 Semi-quantitative classification ability of the three methods for PFO-RLS. (A) cTEE showing high amounts of MBs of contrast agent in the left atrium; (B) cTTE showing high amounts of MBs of contrast agent in the left heart; (C) cTCD showing rain curtains. PFO, patent foramen ovale; RLS, right-to-left shunt; cTEE, contrast transesophageal echocardiography; cTTE, contrast transthoracic echocardiography; MB, microbubble; cTCD, contrast-enhanced transcranial Doppler.

Figure 2). The Spearman analysis showed that the degree of RLS was positively correlated with the inner diameter of the PFO (r=0.695, P<0.001). However, no significant correlation was found between the degree of RLS and the length of the PFO tunnel (r=–0.034, P=0.73) (*Table 4*).

Discussion

The findings of this study suggested that cTCD had a higher sensitivity and semi-quantitative classification capability than cTTE for the diagnosis of PFO. Thus, cTCD has the potential to be a good screening method for PFO. Conversely, cTEE had the highest specificity for diagnosing PFO. Therefore, the combination of cTCD and cTEE could provide a favorable strategy for the diagnosis of PFO.

A meta-analysis (26) showed that the sensitivity rate of cTCD for the diagnosis of PFO was 97%, which was higher than that of cTEE. Li *et al.* (27) showed that the sensitivity rate of cTTE was higher than that of cTEE, while Yang *et al.* (25) showed that the sensitivity rates of cTCD and cTEE were not significantly different and both were higher than that of cTTE, which is generally consistent with our findings. Recently, an *in vitro* and *in vivo* observational study showed that agitated saline with 10% blood increases number and stability of MBs in detection RLS by contrast

Table 4 Correlation of the degree of PFO-RLS with the inner diameter of the PFO and tunnel length

Degree of RLS	PFO inner diameter (mm, mean ± SD)	PFO tunnel length (mm, mean ± SD)
Grade I (low amount)	1.2±0.4	8.8±2.7
Grade II (moderate amount)	2.3±0.6	9.5±2.2
Grade III (high amount)	2.7±0.4	8.9±2.6

PFO, patent foramen ovale; RLS, right-to-left shunt; SD, standard deviation.

enhanced transcranial Doppler. And it showed that both the size and number of MBs were most stable in the agitated saline (AS) with 10% blood (10% BAS), which could be the reasons why the 10% BAS had the highest positive rate and RLS levels in cTCD (28). Our study also showed good repeatability of cTCD with 10% BAS. In the present study, the diagnosis of cTCD resulted in three (2.44%) false negatives and six (4.88%) false positives. The high sensitivity of cTCD may be related to the stable images that are not affected by provocation maneuver and the ability of automated MBs monitoring software to detect small MBs that cannot be monitored by the ultrasonographer with the naked eye; and cTCD does not rely on tomography. False negatives may be related to gravity-mediated alterations in the anatomical relationships of the foramen ovale and the relatively low fractional flow but relatively high number of vascular anastomotic branches in RLS (29). cTCD cannot show the origin of the RLS and it only indirectly determine the origin through the timing of appearance of MBs in the middle cerebral artery (MCA). False positives may be associated with the presence of pulmonary arteriovenous malformations, and the physiologic passing through the lungs during the strong provocation (30). RLS in six false positives were confirmed as pulmonary shunt by cTEE in our study.

The results of this study showed that the diagnosis of cTTE resulted in 13 (10.57%) false negatives and six (4.88%) false positives. The low sensitivity of cTTE may be related to a failure to effectively increase right atrial pressure, poor image quality due to air interference in the lung images, image instability, and the inadequate filling of the right atrial contrast due to an oversized inferior vena cava valve, while the false positives may be related to inadequate contrast elimination from the previous ultrasound examination, and the presence of pulmonary arteriovenous fistula, and the physiologic passing through the lungs during the strong provocation (30-32). RLS in six false positives were confirmed as pulmonary shunt by cTEE in our study.

In the present study, the diagnosis of cTEE was false negative in two cases (1.63%), which could be due to post-intubation stress and inadequate Valsalva motion in both patients, such that the right atrium pressure was not effectively elevated. The cTEE diagnosis did not reveal any false positives. One study reported that the sensitivity and specificity rates of TEE for the diagnosis of PFO were 89.2% and 91.4%, using confirmation by autopsy, cardiac surgery, and/or catheterization as the reference (33). In the present study, in 14 patients, TEE showed no echogenic separation or shunt signal at the site of the interatrial septal foramen ovale, but the cTEE examination clearly showed MBs of contrast in the left atrium from the foramen ovale. The rate of missed diagnosis was 11.38% when PFO was diagnosed by TEE alone. Possible reasons for the missed diagnosis include the PFO being in the state of adhesion, the shunt velocity being too low, or the acoustic beam at the PFO being perpendicular to the blood flow and resulting in a poor display of color flow.

The occurrence of PFO-related diseases is also associated with the fractionation of RLS (34). The results of the present study showed that the semi-quantitative classification of PFO was higher with cTCD than cTTE and was higher with cTTE than cTEE. cTEE underestimated the extent of RLS compared with cTCD and cTTE, which is consistent with the results reported by Yang *et al.* (25). This may be because the cTEE field of view is limited in the left atrium, while cTCD is more accurate, as it uses automated microembolic monitoring software for assessment and does not rely on tomography. However, studies showed that the degree of RLS is not considered to be associated at all with the risk of future cerebrovascular events in patients with PFO (35,36). A correct RLS classification can be considered of minor importance (37).

This study had several limitations. First, the semi-quantitative classification criteria were developed according to findings of previous studies, and the reasonability of the criteria was not further investigated. Second, the raising of the right atrium by Valsalva movement is unlikely to be identical among the three examination methods, which may have led to a bias in the results. Third, the sample size of our study is small, and we will continue to accumulate cases for further research.

Conclusions

In summary, although cTEE used to be the "gold-standard" of diagnosing PFO, and it can identify the anatomical features of PFO and the adjacent atrial septum; it is not a suitable choice for a primary screening test because of its semi-invasiveness. However, cTCD can be chosen as primary screening test because of its high sensitivity, noninvasiveness and repeatability. our study showed the combination of cTCD and cTEE provide a favorable strategy for the diagnosis of PFO. The results of this study might provide important reference values for selecting the best diagnosis strategy for clinicians.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-330/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-330/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-330/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-330/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of The First Hospital of Shanxi Medical University (No. 2021-k-k116). Informed consent was taken from all individual participants.

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Cite this article as: Xu K, Tian X, Hao M, Li Y, Zhang J, Wong RHL, Othmani A, Zhang Q. Diagnostic value of contrast-enhanced ultrasonography for patent foramen ovale detection. J Thorac Dis 2024;16(5):3282-3290. doi: 10.21037/jtd-24-330