Comparison of methods for the diagnosis of patent foramen ovale in patients with cryptogenic cerebral ischemia: a meta-analysis

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Abstract

Background: Foramen ovale is a residual cavity in the developing heart in the fetus. At present, the standard methods for the diagnosis of PFO-right-to-left-shunting (PFO-RLS) include transesophageal echocardiography (TEE), contrast-transcranial Doppler echocardiography (C-TCD), and contrast-transthoracic echocardiography (C-TTE), each of them having its advantages and disadvantages.However, there are no data allowing the comparison of these three methods. Methods: We systematically reviewed all published studies on patients with cryptogenic cerebral ischemia. The sensitivity, specificity, and other indexes of C-TCD and C-TTE in the diagnosis of PFO-RLS were calculated using the Stata 16.0 software. The area under the summary receiver operating curve(SROC) was calculated. Results: Twenty-five 25 controlled studies involving a total of 2282 patients were analyzed. There was considerable heterogeneity between C-TCD and C-TTE sensitivity and specificity among the studies. The combined sensitivity and specificity of C-TCD and C-TTE were 0.95 (95%CI, 0.93-0.97) and 0.86(95%CI, 0.78-0.91), and 0.88 (95%CI, 0.69-0.96) and 0.99 (95%CI, 0.67-1.00). The positive likelihood ratio and negative likelihood ratio of C-TCD and C-TTE were 6.81 (95%CI, 4.42-10.48) and 0.05 (95%CI, 0.03-0.08), and 82.31(95%CI, 2.03-3341.00) and 0.12 (95%CI, 0.04-0.34). The areas under the SROC for C-TCD and C-TTE were 0.97 (95%CI, 0.95–0.98) and 0.98 (95%CI, 0.96–0.99), respectively, and were not significantly different by the Z test (z=-0.17, p=0.86). Conclusion: C-TCD and C-TTE have advantages in diagnosing PFO-RTL. The combination of C-TCD and C-TTE improves the detection rate and reduces the misdiagnosis rate. Key words: patent foramen ovale, cryptogenic cerebral ischemia, contrast-transthoracic echocardiography, contrast-transthoracic echocardiography

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Methods: We systematically reviewed all published studies on patients with cryptogenic cerebral ischemia. The sensitivity, specificity, and other indexes of C-TCD and C-TTE in the diagnosis of PFO-RLS were calculated using the Stata 16.0 software. The area under the summary receiver operating curve(SROC) was calculated.

Results: Twenty-five 25 controlled studies involving a total of 2282 patients were analyzed. There was considerable heterogeneity between C-TCD and C-TTE sensitivity and specificity among the studies. The combined sensitivity and specificity of C-TCD and C-TTE were 0.95 (95%CI, 0.93-0.97) and 0.86(95%CI, 0.78-0.91), and 0.88 (95%CI, 0.69-0.96) and 0.99 (95%CI, 0.67-1.00). The positive likelihood ratio and negative likelihood ratio of C-TCD and C-TTE were 6.81 (95%CI, 4.42-10.48) and 0.05 (95%CI, 0.03-0.08), and 82.31(95%CI, 2.03-3341.00) and 0.12 (95%CI, 0.04-0.34). The areas under the SROC for C-TCD and C-TTE were 0.97 (95%CI, 0.95–0.98) and 0.98 (95%CI, 0.96–0.99), respectively, and were not significantly different by the Z test (z=-0.17, p=0.86).

Conclusion: C-TCD and C-TTE have advantages in diagnosing PFO-RTL. The combination of C-TCD and C-TTE improves the detection rate and reduces the misdiagnosis rate.

Key words: patent foramen ovale, cryptogenic cerebral ischemia, contrast-transthoracic echocardiography, contrast-transthoracic echocardiography

Introduction

Foramen ovale is a physiological opening in the atrial septum in the fetus. After birth, with the development of lungs, the pressure gradient increases from the left to right atrium, and the foramen ovale is functionally and anatomically closed after the age of 3[1]. The incidence of patent foramen ovale (PFO) in adults is about 10%-35% [2]. Moreover, an increasing number of studies show that PFO-right-to-left shunting (PFO-RLS) plays a major role in many diseases, such as a transient ischemic attack, migraine, unexplained cerebral infarction, decompression sickness, and cryptogenic stroke[3]. In comparison with healthy individuals, PFO is more common in young patients with unexplained cerebrovascular events or cryptogenic stroke[4-5]. PFO-RLS can be detected by contrast-transcranial Doppler echocardiography (C-TCD), contrast-transthoracic echocardiography (C-TTE), and transesophageal echocardiography (TEE)[6]. Although TEE has long been seen as the most accurate method for detecting PFO-RLS[7], transesophageal ultrasound is semi-invasive and may lead to false-negative results. Therefore, non-invasive C-TCD and C-TTE are used to screen for PFO-RLS, but the reliability of PFO diagnosis remains controversial[8]. Thus, the purpose of this study was to determine whether C-TCD and C-TTE are effective in detecting PFO in cases of cryptogenic cerebral ischemia, thus providing more effective and simple diagnostic methods.

1.Methods

1.1 Inclusion and exclusion criteria

Inclusion criteria:

(1) the objective of this study was to determine the diagnostic value of C-TCD and C-TTE in cryptogenic cerebral ischemia caused by PFO-RLS;

(2)to have the gold standard: the diagnosis by TEE;

(3)studies reporting the true positive (TP), false-positive (FP), true negative (TN) and false-negative (FN) results of C-TCD and C-TTE in the diagnosis of cryptogenic cerebral ischemia caused by PFO-RLS.

Exclusion criteria:

(1)duplicate publications;

literature that cannot be extracted directly or indirectly from four tables;

(3)reviews articles and case reports;

(4)animal experiments.

1.2 Retrieval strategy

Electronic databases such as PUBMED, EMBASE, Cochrane Library, Chinese Biomedical Literature Database, China National Knowledge Infrastructure, and Wanfang Data were searched from their inception to November 30, 2020, using the following keywords: transcranial Doppler contrast echocardiography, C-TCD, C-TTE, transthoracic echocardiography, cerebral ischemia, transient ischemic attack, patent foramen ovale, PFO, right-to-left shunt.

1.3 Data collection

Two researchers extracted the data independently, and a difference in opinion was resolved by the third researcher. During the screening of the literature, the title and abstract were read first to exclude irrelevant publications, and then the full text was evaluated to determine the inclusion in the study. In case of missing information, an attempt was made to obtain complete data from the original author, and if this was not possible, the study was excluded. The extracted information included the author's name, publication time, true positive (TP), false-positive (FP), true negative (TN), and false-negative (FN).

1.4 Quality evaluation

QUADAS-2, a tool for evaluating the accuracy of diagnostic tests, and the ReviewManager 5.4 software were used independently by two reviewers to evaluate the quality of publications and generate the literature quality evaluation form.

1.5 Statistical analysis

The combined sensitivity, specificity, positive and negative likelihood ratios, and 95% confidence interval were calculated using the Stata 16.0 software. Subsequently, the areas under the SROC of C-TCD and C-TTE were compared by z-test. $P < 0.05$ was considered to reflect a statistically significant difference between two groups. I2 value was used to evaluate the heterogeneity of the study. If the I2 value was <50%, moderate heterogeneity was assumed, and a meta-regression analysis was performed to explore potential sources of heterogeneity. The funnel chart was used to evaluate the publication bias.

2 Results

2.1 Study Selection and Study Characteristics

A total of 2161 articles were retrieved from Medline, EMBASE, Cochrane Library Database, China Biomedical Literature Database, China National Knowledge Infrastructure, and Wanfang Database. After excluding 1789 studies, such as editorials, letters, responses, reviews, and case reports, 70 studies that had the potential to meet the criteria of the meta-analysis were retained. By searching their full text, 45 of them were excluded since they addressed only non-PFO-RLS cases or had an inadequate design. In the end, 25 studies were included in the present meta-analysis (Figure 1).

2.2 Quality Assessment

Among the 25 articles included in this study, 7 utilized TEE as the gold standard, and the remaining 18 articles utilized C-TEE (Fig. 2 and 3). In 15 studies (60%), patients with IS/TIA were selected continuously and were not inappropriately excluded after the initial recruitment. In the remaining 10 studies, the risk of patient selection bias was not clear since patient recruitment was not adequately reported.

2.3 Quantitative Analysis

C-TCD was used as the index in 22 articles, c-TTE as the index in 5, and both C-TCD and C-TTE in 2 (Table 1). The diagnostic accuracy of the studies is listed in Table 2. There was considerable heterogeneity between C-TCD and C-TTE sensitivity and specificity studies. The combined sensitivity and specificity of

C-TCD and C-TTE were 0.95 (95%CI, 0.93-0.97) and 0.86 (95%CI, 0.78-0.91), and 0.88 (95%CI, 0.69-0.96) and 0.99 (95%CI, 0.67-1.00) (Fig. 4 and 5). The positive and negative likelihood ratios of the C-TCD and C-TTE groups were 6.81 (95%CI, 4.42-10.48) and 0.05 (95%CI, 0.03-0.08), and 82.31 (95%CI, 2.03-3341.00) and 0.12 (95%CI, 0.04-0.34) (Fig. 6 and 7). The areas under the SROC curve (AUC) of the C-TCD and C-TTE were 0.97 (95%CI, 0.95-0.98) and 0.98 (95%CI,0.96–0.99). There was no significant difference in the AUC between C-TCD and C-TTE by the Z test (z=-0.17,p=0.86) (Fig. 8 and 9)

Next, subgroup analysis was conducted to explore the potential source of heterogeneity in the C-TCD group. The Insonation method was identified as the specific source of heterogeneity, and the number of patients number was the heterogeneity source for sensitivity (Table 3). Since only 5 articles included the C-TTE group, subgroup analysis was not performed.

2.4 Publication bias.

The Deek's method did not identify publication bias (p=0.77 for C-TCD; p=0.25 for C-TTE)(Fig. 10 and 11).

3 Discussion

Stroke has severe health consequences and generates a significant financial burden to the family of the patient. Approximately 20%-30% of ischemic stroke instances are cryptogenic. their etiology involves many possible hidden mechanisms[9]. Studies have shown that PFO is associated with a transient ischemic attack, migraine, unexplained cerebral infarction, decompression sickness, and cryptogenic stroke, and the probability of PFO complicated with these diseases is much higher than in normal people[10-11].In contrast to the case-control study of Sophie et al., which only reported the incidence of PFO in ischemic stroke patients younger than 55 years old, Handke et al. divided patients into young and old, using 55 years as the threshold. Both analyses showed that PFO was independently related to the embolic stroke of undetermined origin (ESUS)[12-13]. Therefore, increased attention has been paid to the detection of PFO. Another study has found that about 50% of CS patients with PFO exhibit a significant correlation, and these patients are typically relatively young[14]. With the wide application of transcranial Doppler foaming test (contrast TCD, C-TCD) and transesophageal echocardiography (TEE), the detection rate of PFO has been significantly improved.

At present, C-TEE is considered the most accurate method for diagnosing PFO since it can evaluate atrial structure more closely, more intuitively, and more clearly due to avoiding the interference of chest wall, lung gas, and other factors. The positive rate of PFO detection can reach 82.6%[15]. However, TEE is a semi-invasive examination with a complex operation and many complications and contraindications, such as esophageal bleeding, perforation, esophageal varices, Barrett esophagus, and the risk of severe bleeding. These factors prevent the wide clinical use of C-TEE[7]. In recent years, an increasing number of clinicians choose C-TCD for PFO screening because this technique is non-invasive, safe, simple, and easy, and the Valsalva action can improve the detection rate. However, the disadvantage of C-TCD is that it can only detect the presence of a shunt without establishing whether the embolus is from the heart or lung [16]. C-TTE can more directly display the cardiac structure, including the size of the foramen ovale. Moreover, C-TCD and C-TTE, with their advantages of low price, simplicity, convenience, and reproducibility, are more frequently used than C-TEE and became reliable methods for detecting PFO-RLS.

Caputi et al. showed that compared with C-TEE, C-TCD has higher sensitivity and specificity in the diagnosis of cryptogenic cerebral ischemia or transient cerebrovascular disease in patent foramen ovale[17]. The current meta-analysis also indicates that the sensitivity of C-TCD in detecting patent foramen ovale in patients with cryptogenic cerebral ischemia was higher than that of C-TTE (0.95 vs. 0.88), although the specificity was lower (0.86 vs. 0.99). The positive predictive value of C-TCD was also lower than that of C-TTE (6.81 vs. 82.31), indicating that the C-TTE-based diagnosis of PFO is more reliable. Conversely, the negative predictive value of C-TCD was significantly lower than that of C-TEE (0.05 vs. 0.12), suggesting that negative C-TCD can accurately exclude PFO. The above results suggest that c-TCD has higher sensitivity and lower specificity for RLS detection than C-TTE, which is consistent with the study of Zhao Enfa et al. [18]. Given the high sensitivity and low specificity of the c-TCD test, our research team reached the following conclusions. First, the patient cannot remain immobile when performing Valsalva, which affects the quality of the TTE image and decreases the positive rate of c-TTE examination. Second, in c-TTE inspection, the number of microbubbles is statistically recorded in a certain section, while the c-TCD inspection process is assisted by monitoring software, making it is more objective and accurate. Third, the RLS detected by TCD includes not only intracardiac but also extracardiac RLS. For the detection of PFO-RLS, c-TTE is more specific than c-TCD because it is based on the examination of cardiac structure and can differentiate between intracardiac and extracardiac RLS. Together, these findings document that both C-TTE and C-TCD have high diagnostic value in cryptogenic cerebral ischemia caused by PFO-RLS. At the same time, the AUC did not differ significantly between C-TCD and C-TTE (0.97 vs. 0.98). However, when diagnosing PFO-RLS with C-TCD, patients must cooperate with the Valsalva maneuver and other auxiliary actions that can transiently increase right atrial pressure, which can lead to a difference in the sensitivity of PFO-RLS detection sensitivity of up to 40%-50% [19-20]. The study of Yang et al. demonstrated that combining C-TCD with C-TTE significantly improved the specificity and significantly decreased the rate of misdiagnosis, implying that the combined examination is essential in screening patients with suspected PFO [8]. Together with the results of the present meta-analysis, these findings suggest that C-TCD has a higher sensitivity in the diagnosis of PFO-RLS in patients with cryptogenic cerebral ischemia, and C-TTE has higher specificity in the diagnosis of PFO-RLS. Moreover, the combination of C-TCD and C-TTE improves the detection rate and reduces the misdiagnosis rate.

Therefore, our conclusion is that the combination of c-TCD and c-TTE examinations has the advantages of non-invasiveness, safety, and significant clinical maneuverability and improves the sensitivity and specificity of the diagnosis of PFO-RLS. To some extent, TEE can be used as an effective hand segment for PFO-RLS screening. Cryptogenic stroke patients with c-TCD positive, c-TTE negative or c-TCD negative, c-TTE positive can be further examined by TEE and lung CTA to determine the cause.

Conflict of interest: Xiaoxuan Guo Xiaojuan Wang Lu Zhang Yan Zhang Rui Peng Haiye Gao Aiyun Deng declare that they have no conflict of interes.

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