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Original Article

Clinical value of cryptogenic stroke associated with small patent foramen ovale detected jointly by TEE and cTCD

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Abstract: Objective: To observe and evaluate the clinical value of transesophageal echocardiography (TEE) combined with contrast transcranial Doppler (cTCD) in detecting cryptogenic stroke (CS) associated with small patent foramen ovale (PFO). Methods: Thirty-two patients with CS associated with small PFO admitted from February 2016 to May 2017 were selected in this study. All of them were proved to have cryptogenic stroke focus by skull CT or MRI. TEE, cTCD and TEE combined with cTCD were used respectively to conduct detection. Results: Among the 32 patients, 20 positive cases (62.5%) were detected by TEE; 19 positive cases (59.4%) were detected by cTCD, and 27 positive cases of CS associated with small PFO (84.4%) were detected by TEE combined with cTCD. The small PFO detection rate by TEE combined with cTCD was significantly higher than that by TEE group or cTCD group (both $P<0.05$). PFO slit width measured by TEE is 0.7-2.0 (1.5±0.4) mm, which was better than cTCD. The detection rate of right-to-left shunt by TEE combined with cTCD was significantly higher than that by TEE or cTCD, moreover, in comparison with TEE, the detection rate of right-to-left shunt by cTCD has increased remarkably ($P=0.000$). There was no obvious differences in the PFO detection rate conducted by TEE combined with cTCD under the states of quiet breathing and Valsalva ($P=0.768$). Conclusion: TEE combined with cTCD can improve the detection rate of potential cardiogenic etiology of CS associated with small PFO and that has important clinical value in guiding the choice of CS treatment method.

Keywords: Transesophageal echocardiography, contrast transcranial Doppler, small patent foramen ovale, cryptogenic stroke

Introduction

Among the adults, there are 20% to 25% people with patent foramen ovale (PFO) which was the most common congenital heart abnormalities in adults. PFO has close relationship with stroke patients caused by unknown reasons whose age are less than 55 years old [1]. In recent years, a large number of studies have shown that patent foramen ovale and atrial septal aneurysm constitute one of the important causes of cryptogenic stroke (CS). Therefore, the diagnosis of PFO has great value in the etiological analysis of CS and may influence the choice of treatment options.

At present, there are many kinds of ultrasonic diagnostic techniques for PFO. How to effectively master the advantages and disadvantages of various techniques and apply them reasonably is the key to the PFO diagnosis. Currently, the echocardiography used frequently in the clinic includes transthoracic echocardiography (TTE), transesophageal echocardiography (TEE) and contrast transcranial Doppler (cTCD) [2]. TTE has low sensitivity on finding PFO in common crowd, and TTE is susceptible to the disturbance of patient's body shape or gas, such as obesity and emphysema [3]; thereby, TTE cannot observe the structure of PFO and abnormal blood flow condition well, but can easily miss diagnose some patients who do not have obvious atrium level shunt. But TTE has the biggest advantage of noninvasive examination and easy acceptance of patients. TEE is an invasive examination method for structure deformity within heart. Some studies have shown that the diagnostic accuracy of TEE

for PFO is better than that of MRI [4]. However, patients feel uncomfortable and painful and have poor compliance during TEE operation, so TEE cannot accurately provide information about craniocerebral complications [5]. cTCD examination has the advantage of simplicity and noninvasiveness and is more sensitive to right-to-left shunting detection of PFO and see the influence of PFO towards cranial circulation. However, cTCD cannot provide anatomic locations of right-to-left shunting or other cardiac structural abnormalities [6]. Obviously, the three kinds of ultrasound techniques have their own advantages and disadvantages.

TEE combined with cTCD brings their respective advantage into play, and makes up for each other's deficiencies. In diagnosis of PFO, cTCD shows more advantages on the basis of imageological examination like TEE to exclude the system or pulmonary circulation problems such as ventricular defect, atrial septal defect, arteriovenous fistula. Studies have shown that cTCD cavitation technology can reach 100% of specificity and sensitivity towards right-to-left shunting of atrium level [7]. Currently, there are few reports on the application value of TEE combined with cTCD in detecting CS caused by small PFO, therefore, this study compared and analyzed TEE and cTCD examinations of CS associated with PFO so as to provide experimental evidence for clinical diagnosis.

Materials and methods

General materials

The study was approved by the Ethics Committee of Luoyang Central Hospital Affiliated to Zhengzhou University, and patients and their families were aware of this diagnosis and treatment plan, and they all signed to confirm.

Thirty-two patients with CS associated with PFO treated in our hospital from February 2016 to May 2017 were selected. All patients underwent TEE and cTCD examination. And the existence of CS lesions was confirmed through the head CT or MRI and other causes of CS were excluded.

Among the patients, there were 25 males and 7 females, their age ranged from 22 to 64 years old with an average age of 42.7±12.5 years old; 17 patients with history of hypertension, 3 patients with history of diabetes, 5 patients with history of hyperlipidemia, 20 patients with history of smoking and 13 patients with history of drinking.

Diagnostic method

Transesophageal echocardiography (TEE): The Philips IE33 model color Doppler ultrasound instrument was used at a frequency of 2-4 MHz to detect whether or not the atrial septum has fracture on the location of fossa ovalis through the multi-section of the transesophageal probe. The diagnostic criteria were: fracture width greater than 4 mm is large PFO, fracture width 2-4 mm is middle PFO and fracture width less than 2 mm is small PFO. At the same time the doctor shall determine whether there is right to left shunt.

Transcranial Doppler echocardiography (c-TCD): The TC 8080 model transcranial Doppler ultrasound instrument from German EME was used at a frequency of 1.6 MHz. Quantitative grading was conducted according to the number of microvesicle and bilateral grading standards are as follows: 0 micro-embolus signal is level I; 1 to 20 micro-embolus signals (one side is 1-10) is level II; over 20 micro-embolus signals (>10 on one side) with non-curtain shape is level III; the micro-embolic signal with rain-curtain type or shower type is level IV [8].

The judgment standard of TEE and cTCD joint detection is that any examination in TEE and cTCD tests positive.

Observation index

Compare and analyze the PFO fracture width, PFO detection rate and right-to-left shunt among the three detection methods.

Statistical treatment

SPSS23.0 statistical software package was used to conduct statistical treatment towards the observation result. All measurement data were expressed as mean ± standard deviation; comparison among groups used independent samples t test. Enumeration data were expressed by case number and percentage rate; the comparison among groups was tested by χ^2. $P<0.05$ indicates that the difference is statistical significance.

Table 1. Comparison of the effect of three detection methods

Detection method	Case	Positive (n, %)	Negative (n, %)
TEE	32	20 (62.5)	12 (37.5)
cTCD	32	19 (59.4)	13 (40.6)
TEE combined with cTCD	32	27 (84.4)*,#	5 (15.6)*,#

Note: TEE, transesophageal echocardiography; cTCD, contrast transcranial Doppler. Compared with TEE detection, *χ^2=3.925, *P=0.048; compared with cTCD detection, #χ^2=4.947, #P=0.026.

Table 2. The relationship between three methods and PFO shunting

Detection method	Right-to-left shunting (+)	Right-to-left shunting (-)
TEE	0	32
cTCD	16	16
TEE combined with cTCD	24	8
χ^2	38. 40	
P	0.000	

Note: PFO, patent foramen ovale; TEE, transesophageal echocardiography; cTCD, contrast transcranial Doppler.

Table 3. Analysis of PFO results detected by TEE combined with cTCD

Projects	+	-
Calm state	24 (75.0)	8 (25.0)
Valsalva maneuver	25 (78.1)	7 (21.9)
χ^2	0.087	
P	0.768	

Note: PFO, patent foramen ovale; TEE, transesophageal echocardiography; cTCD, contrast transcranial Doppler.

Results

Comparison on the diagnosis of PFO positive rate by using three detection methods

Analyze and summarize the basic clinical materials of 32 patients, in the quiet respiratory state, TEE had checked out 20 positive cases (62.5%); cTCD had checked out 19 positive cases (59.4%); TEE combined with cTCD had checked out 27 CS-related PFO positive cases (84.4%); the positive rate of TEE combined with cTCD is remarkably higher than that of TEE or cTCD (both P<0.05), while the difference between positive rates of TEE and cTCD on PFO showed no statistical significance (P=0.798). See **Table 1**.

The positive rate comparison on PFO right-to-left shunt among the three detection methods

The PFO fracture width measured by TEE was 0.7-2.0 (1.5±0.4) mm. cTCD can't measure the fracture width of PFO effectively. On the detection of PFO fracture width, TEE was superior to cTCD. On right-to-left shunt testing, the positive rate of TEE combined with cTCD was significantly higher than that of TEE or cTCD. Compared with TEE, the positive rate of right-to-left shunt by cTCD was significantly higher (P=0.000). See **Table 2**.

The comparison of different TEEs combined with cTCD

In the quiet respiratory state, 24 PFO cases (75.0%) had been checked out by TEE combined with cTCD and after Valsalva maneuver, 25 PFO cases (78.1%) had been checked out by TEE combined with cTCD; the difference of PFO positive rate under these two states has no statistical significance (P=0.768). See **Table 3**.

Discussion

The right-to-left shunt produced by PFO leads to paradoxical embolism, which may be the cause of CS and has been confirmed in some cases [9, 10]. PFO is often accompanied by atrial septal aneurysm which may cause thromboembolism [11]. Although no randomized prospective study is currently available, the recurrence risk of cerebral embolism increases fivefold on PFO patients who have the first-time cerebral embolism history, especially on those complicated with atrial septal aneurysm [12, 13].

TEE places a special transesophagel probe in the esophagus or fundus and scans the heart forward from behind the heart [14]. It not only overcomes the limitations of transthoracic ultrasound images affected by emphysema, obesity, thoracic deformity and other factors, but also greatly improves diagnostic sensitivity and specificity of some heart disease since the esophageal probe adjacent to the left atrium can clearly show the microstructure of the posterior structure of the heart [15]. In particular for patients with mitral stenosis, 50% of this kind of patients has spontaneous acoustic shadow in the left atrium. Due to blocked blood flow and rouleau formation accu-

mulation, the blood echo has intensified. This kind of patients has a higher risk of thromboembolism, 20% to 30% of patients with spontaneous acoustic shadow have formed left atrial thrombosis. Other left atrial structural abnormalities that increase the risk of thrombosis formation include atrial septal defect, PFO and atrial septal aneurysm [16]. Constant transcranial Doppler (cTCD) is a noninvasive technique that uses ultrasound to examine intracranial great vessel blood flow velocity. In recent years more and more attention has been paid to this technique by clinicians. cTCD examination of PFO has the advantages of noninvasiveness, simplicity, repeatable examination and high sensitivity and currently this technique is widely used in the etiology diagnosis of patients with transient ischemic attack, cryptogenic cerebral stroke and migraine. Some studies have shown that cTCD is a precise detection method for patent foramen ovale and its specificity and sensitivity is only next to TEE [17]. Another study has shown cTCD sensibility towards PFO right to left shunt is not inferior to TEE radiography [18]. Our results showed that PFO fracture width measured by TEE was 0.7-2.0 (1.5±0.4) mm. Among 32 patients, TEE had detected 20 positive cases (62.5%); cTCD had detected 19 positive cases (59.4%), the positive rate of TEE combined with cTCD (27 cases, 84.4%) was significantly higher than that of TEE or cTCD. The PFO detection of TEE combined with cTCD in the Valsalva state was slightly higher than that in the calm breathing state, which may due to that Valsalva maneuver can make the right heart pressure increase, thereby increasing the probability and area of oval foramen opening so as to improve the positive detection rate [19].

cTCD application of cavitation technology can improve the examination sensitivity of interatrial right to left shunt. Some study has shown that cTCD is superior to intracardiac echocardiography in detecting right-to-left shunting of PFO [20]. Another study reported that in the cTCD test the middle cerebral artery was found to have microvesicle signals but there was no intracardiac right-to-left shunt in the TEE test [21]. It is likely that cTCD not only can detect microvesicle signals in the middle cerebral artery right-to-left shunted from intracardiac, but also can detect right-to-left shunt in the lung [22]. The results of this study showed that the positive rate of TEE combined with cTCD for the PFO detection was significantly higher than that of TEE and cTCD, indicating that TEE could compensate the deficiency of cTCD. When the fractional flow of the PFO is very small, the microvesicle signal may momentarily flow within the left heart system, diffuse across the arterial branches of the aortic arch and the descending aorta, enter the intracranial artery without passing through the internal carotid artery, thus no microvesicle signal can be detected in middle cerebral artery.

In summary, TEE combined with cTCD can improve the detection rate of potential cardiogenic etiology of CS-related small PFO and provides important reference for further treatment as TEE combined with cTCD detection has important clinical value in the diagnosis and treatment of CS-related small PFO. However, this study has some limitations such as small sample size and this is a single-center study, therefore the conclusion needs further confirmation in future research.

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Disclosure of conflict of interest

None.

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