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Prevalence of Patent Foramen Ovale and Diagnostic Efficacy of Transcranial Doppler Sonography in Cryptogenic Ischemic Stroke Patients

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The prevalence of patent foramen ovale (PFO) in healthy persons was estimated as about 10~25% and was up to 40% in patients with stroke. Transesophageal echocardiography (TEE) was considered to be the most sensitive method to detect PFO and was used as the gold standard. Transcranial doppler sonography (TCD) of the middle cerebral artery (MCA) during a contrast (saline bubble) injection has recently been proposed as an alternative detecting method for PFO. In this study, we would like to know the difference between TCD value and TEE value in subjects with cryptogenic ischemic stroke. We performed TCD and TEE tests to detect PFO on 64 patients (30 women and 34 men, mean age was 59.4 years) with cryptogenic ischemic stroke. PFO prevalence through TCD was 45.3% (29 of 64 patients) and the prevalence through TEE was 34.4% (22 of 64 patients). There was no statistical significance between PFO test and TCD test (P=0.206). But TCD had a sensitivity of 90.9% (20 of 22 patients), specificity of 78.6% (33 of 42 patients), positive predictive value of 69.0% (20 of 29 patients), and negative predictive value of 94.3% (33 of 35 patients). We concluded that TCD was a highly sensitive method for detecting a right-left shunt. Therefore, the non-invasive TCD test is a method more effective than the anti-invasive TEE test in the cost and evaluation of the existence or nonexistence of right to left shunt in addition to the screening method of the cerebrovascular disorder. Considering these points, TCD test could be recommended for patients with cryptogenic ischemic stroke as a useful and convenient method for screening of the existence or nonexistence of a right to left shunt caused by PFO.

Key Words: Patent foramen ovale (PFO), Cryptogenic ischemic stroke, Transesophageal echocardiography (TEE), Transcranial doppler sonography (TCD)

INTRODUCTION

The foramen ovale in the interatrial septum of heart is open because of the functional inactivity of fetal lungs. Fetal blood of the inferior vena cava is mostly transported from the right atrium to the left atrium. After birth, the foramen ovale is closed because of the increase of the left atrial pressure and decrease of the right atrial pressure. But in 10~25% of adults, patent foramen ovale (PFO), a phenomenon that the foramen ovale is not closed is appeared and it is one cause of atrial septal defects (Lechat et al., 1988).

It was reported in the west that the rate of PFO was 10~35% in adults (Hagen et al., 1984; Lynch et al., 1984) and got increased in patients with a stroke and transient ischemic attack (ministroke) (Lechat et al., 1988). Especially, 35% of ischemic cerebrovascular diseases occurring in young adults have an unknown cause and the paradoxical embolism by PFO is conjectured as one of the causes (Jones et al., 1983).

The paradoxical embolism occurred because a thrombus formed by PFO in the venous system was not trapped by the pulmonary system and transferred to the left atrium from the right atrium through a right-left shunt. It is known as one cause of cryptogenic ischemic stroke. It has reported

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that PFO prevalence in patients with cryptogenic ischemic stroke is 40% more than in normal men (Hagen et al., 1984; Anzola et al., 2004). Therefore, because cryptogenic ischemic stroke is a disease which can be prevented and cured, the test for the diagnosis of PFO has a highly clinical significance.

The diagnosis of PFO syndrome by non-invasive methods was very difficult but the interest in the non-invasive methods increased after developing of the contrast echocardiography. The diagnosing methods for PFO syndrome using the contrast-enhanced transthoracic echocardiography (TTE) have been reported (Lynch et al., 1984; Rodgers et al., 1984) but the domestic research was rare (Chang et al., 2005).

In the contrast-enhanced TTE test, the resolving power was different according to patients and patients might have ischemic cerebrovascular diseases because the existence or nonexistance of thrombus in the left atrial appendage could not detected correctly. But in clinical research, the contrast-enhanced transesophageal echocardiography (TEE) has a good resolution without the patient's condition and can detect exactly the structure of heart with the left atrial appendage and diagnose accurately the cause of an embolism like thrombus of the left atrium. But TEE test as anti-invasive method has a restriction in that it is demands patients' help and it can't be performed if patients have a swallowing problem (Lynch et al., 1984).

Since Teague and Sharma introduced the contrast-enhanced transcranial Doppler (TCD) at first in 1991 year, TCD as a non-invasive test has been used broadly in the diagnosis of PFO because it has the inspective sensitivity and peculiarity (Siostrzonek et al., 1991; Teague et al., 1991).

In our study, we wanted to check whether PFO plays a significant role as an etiological cause in patients with ischemic stroke by investigating the prevalence of PFO. We investigated the existence or nonexistence of PFO in patients with latent ischemic strokes by using TEE and TCD test and a difference between TEE and TCD test. Furthermore, we wanted to verify the availability of TCD for PFO screening by investigating the sensitivity and peculiarity of TCD for the diagnosis of PFO based on the gold standard of TEE.

MATERIALS AND METHODS

1. Subjects

To investigate the prevalence of patent foramen ovale (PFO), we selected patients who were treated with the hospital stroke care in the department of neurology of Seoul National University Bundang Hospital from March, 2004 to February, 2005. We classified strokes according to the criteria of TOAST, Trial of Org 10172 in Acute Stroke Treatment. And we performed tests on the patients who were diagnosed as having cryptogenic ischemic stroke by the retrospective method.

TEE and TCD test for PFO diagnosis were performed on 64 cases out of 248 patients with cryptogenic ischemic stroke. The control group of 23 patients who had not a past history and symptoms were examined by TEE and TCD screening test for the cranial vessel. To investigate the accuracy for PFO diagnosis, we performed TCD test on 64 patients and compared TCD results with TEE results.

2. Method for PFO diagnosis

Two-channel 2 MHz TCD equipments (Pioneer TC 8080, Nicolet Vascular, Madison, Netherlands) were used for the diagnosis of PFO. The contrast solution for the contrast enhancing contained 0.9% NaCl, 1 ml of air, and 0.5 ml of patient's venous blood. Patients were put to bed in the supine position. We used two channels which could inspect both temporal windows and detected the bloodstream spectrum of the right and left middle cerebral artery (MCA) in 40~60 mm depth by using two depth methods with 10 mm interval, and then the probe was fixed by the fixation head frame. We inserted a 21G needle into the antecubital vein of the patients and connected 3-way stopcock, and air bubbles were formed by agitating the contrast solution between two needles. The contrast solution containing air bubbles was administered to patients by Valsalva maneuver (stopping a breath for over 5 seconds after the maximum expiration). And then we monitored the embolic signals from both MCAs during 30 seconds shortly after administering the contrast solution. Embolic signals are the hyper-intensive signals more intensive than background signals by 5 dB and

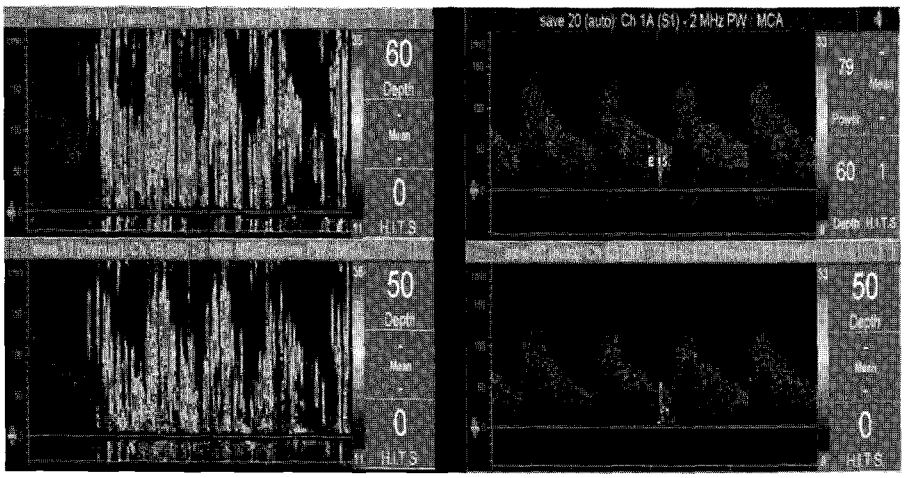

Fig. 1. HITS (right) and multiple HITS in MCAs of a patient (left) by Two-channel TCD.

are defined as the hyper-intense transient signals (HITS) with an ununique sounds and wave forms showing the hyper-intense signal for a short of time. So we reconfirmed embolic signals detected automatically by the testing equipment (Fig. 1). When we could not detect embolic signals, we performed the test repeatedly after taking a rest of 2 minutes (Jauss et al., 2000).

We used transesophageal echocardiography (TEE), 5 MHz gastroscope of Sonos 7500 (Philips, Amsterdam, Netherlands). Patients starved for at least 6 hours before TEE test and were administered 5 mg of diazepam by using an intravenous injection, and treated with the local anesthesia of the laryngopharynx using the solution of benocarine. When a patient lied on his/her left side with the head resting comfortably on a pillow and keeping a mouth-guard, the inspector passed over the gastroscope with the ultrasonic equipment into the esophagus and fixed the probe on the upper position of the esophagus and stomach. And then the test was performed after obtaining a short axis view or four chamber view for detecting the septum of heart and foramen ovale.

The preparation and administration of the contrast solution for contrast enhancing processed the same methods as TCD. We judged that the contrast medium was administered properly when the right atrium was filled completely with the contrast solution. We evaluated a patient as PFO positive when air bubbles were detected in the left atrium within 5 cardiac cycles after administering the contrast solution (Fig. 2) (Lee et al., 1994).

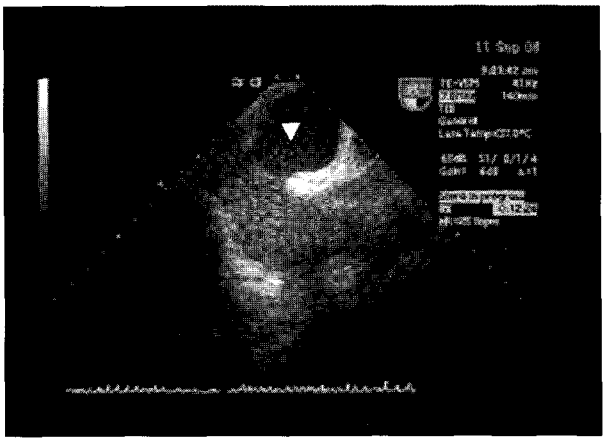

Fig. 2. Transesophageal echocardiography (TEE) showing a small right to left shunt.

3. Analysis of data

By using Pearson's Chi-Square test, we analyzed the prevalence of PFO between the control and patient groups with cryptogenic ischemic stroke and the rate of PFO positive between TCD and TEE. Statistic analysis was performed by using the SPSS 10.07 program and the statistic significant of data was below 5%.

RESULTS

1. The characteristics of the subjects

To investigate the PFO prevalence, we separated the normal control group [male 14 (60.9%) and female 9 (39.1%)] and the patient group [male 34 (53.1%) and female 30 (46.9%)] with cryptogenic ischemic stroke. The

Table 1. Age distribution of the control and patient group

Variables		No. of the patient group (%)	No. of the control group (%)
Sex	Male	34 (53.1)	14 (60.9)
	Female	30 (46.9)	9 (39.1)
Age	<40	1 (1.6)	1 (4.3)
	40~49	8 (12.5)	6 (26.1)
	50~59	19 (29.7)	11 (47.8)
	60~69	22 (34.4)	5 (21.7)
	≧70	14 (21.9)	0 (0.0)

Table 2. The prevalence of patent foramen ovale between the control and patient group

Variables	No. of the patient group (%)	No. of the control group (%)	*P*-value
PFO positive	29 (45.3)	4 (17.4)	0.018*
PFO negative	35 (54.7)	19 (82.6)	

*P<0.05, Values are mean ± SD

normal control group consisted of 50 age (47.8%), 40 age (26.1%), 60 age (21.7%), and below 40 age (4.3%) and the patient group with cryptogenic ischemic stroke consisted of 60 age (34.4%), 50 age (29.7%), over 70 age (21.9%), and 40 age (12.5%), and below 40 age (1.6%) (Table 1).

2. The comparison of PFO prevalence between the control group and the patient group

PFO positive in TCD test was shown in 4 case out of 23 men and 29 cases out of 64 men in the normal control group and the patient group respectively. The prevalence of PFO was 17.4% and 45.3% in the normal control group and the patient group respectively. PFO prevalence in the patient group was higher than that in the control group and statistical significance was shown by using Pearson's Chi-Square test (P=0.018) (Table 2).

3. The comparison of the accuracy of PFO diagnosis between TCD test and TEE test

PFO positive was 22 cases (34.4%) in TEE test and 29 cases (45.3%) in TCD test out of 64 patients and the rate of PFO positive was higher in TCD test than in TEE test. But there was no statistical significance between TCD test and TEE test by Pearson's Chi-Square test (Table 3).

To know the accuracy of PFO diagnosis, we compared

Table 3. The positive rate of Patent Foramen Ovale by TEE and TCD test

Variables	No. of TCD test (%)	No. of TEE test (%)	*P*-value
PFO positive	29 (45.3)	22 (34.4)	0.206
PFO negative	35 (54.7)	42 (65.6)	

*P<0.05, Values are mean ± SD

Table 4. The comparison of the positive rate of PFO between TCD and TEE test

TCD \ TEE	PFO positive (+)	PFO negative (−)	Total
PFO positive (+)	20	9	29
PFO negative (−)	2	33	35
Total	22	42	64

*Sensitivity = (20/22) × 100 = 90.9%
*Speciticity = (33/42) × 100 = 78.6%
*Positive predictive value = (20/29) × 100 = 69.03%
*Negative predictive value = (33/35) × 100 = 94.3%

the result of TCD test with that of TEE test used as the gold standard.

20 out of 22 patients with PFO positive in TEE test was PFO positive in TCD test and PFO diagnosing sensitivity of TCD was 90.9%, and 33 out of 42 patients with PFO negative in TEE test was PFO negative in TCD test and PFO diagnosing specificity of TCD was 78.6%. Therefore 20 out of 29 patients with PFO positive in TCD test was PFO positive in TEE test and the positive predictive value of TCD was 60.9% and 33 out of 35 patients with PFO negative in TCD test was PFO negative in TEE test and the negative predictive value of TCD was 94.3% (Table 4).

DISCUSSION

Hagen et al. (1984) have reported that PFO prevalence was 25% in the autopsy on patients without the history of heart disease and it was higher than 10~18% in the test using the contrast transthoracic echocardiography. But recently, transesophageal echocardiography (TEE) detecting images of the rear structure of the heart such as an atrium and atrioventricular valve have been used broadly. Konstadt et al. (1991) have reported that TEE test was very useful for PFO screening because PFO prevalence in TEE test was 26%.

The paradoxical embolism occurred because a thrombus

formed by PFO in the venous system was not trapped by the pulmonary system and transferred to the left atrium from the right atrium through a right-left shunt. The frequency rate of the paradoxical embolism was different according to reporters but its clinical significance was very high considering a disease which could be prevented and cured. Therefore if we want to find causes of the cerebral infarction and embolism using echocardiogaphy, we should investigate the existence or nonexistence of PFO at first. Especially, it was reported that the frequency of PFO in patients with cryptogenic ischemic stroke was 40% (Onorato et al., 2003; Anzola et al., 2004). Chang et al. (2005) have reported that PFO was 21% in TCD test. In our study, we also investigated the frequency of PFO in patients with the cryptogenic ischemic stroke using TCD which was pain free and non-invasive way to diagnose a PFO. In the result of TCD test, the rate of the PFO positive was 17.4% in the normal control group and 45.5% in the patient group with a latent cryptogenic ischemic stroke, and the rate of the PFO positive in the patient group was higher than the control group by 27.9%. The prevalence of PFO between the patient and control group showed statistical significance (P=0.018). These results demonstrated that PFO was a leading cause of cryptogenic ischemic stroke. So we consider that the accurate diagnosis of PFO is very important in the therapy and prevention of cryptogenic ischemic stroke (Lechat et al., 1988).

Kronik et al. (1982) have reported in the PFO diagnosis that when M-mode transthoracic echocardiography (TTE) test was performed in the conditon of steady state and Valsalva maneuver, PFO appeared only in 64% of patients with PFO and the pressure of the right atrium in the cardiac catheterization. Lechat et al. (1988) have reported that the PFO prevalence of the normal men was 10% in B-mode TTE and this was very different from that in the autopsy, and so TTE was not useful in the diagnosis of PFO considering its sensitivity. Seward et al. (1988) have reported that unlike TTE, transesophageal echocardiography (TEE) was widely used in the hospital after 1990 years and it had a merit to take the concrete pictures of the interatrial septum and atrium in the rear portion of heart. It was reported that unlike TEE, the accuracy of the PFO diagnosis by TCD was 68~100% (Jauss et al., 2000) and when the right to left shunt inducing method and the contrast enhancing were used, the sensitivity, specificity and accuracy of the PFO diagnosis increased up to 91%, 93%, and 93% respectively (Klotzsch et al., 1994). Also we thought that TCD was a very useful in the diagnosis of PFO considering a technical convenience, non-invasive way and unexpensive cost.

Unlike TEE directly detecting air bubbles transferred from the right atrium to the left atrium through foramen ovale, TCD detecting air bubbles in MCA (Sacco et al., 1993) could not differentiate patient foramen ovale (PFO) and atrial septal defect (ASD), and it was a difficult to eliminate the possibility of the fistula of the pulmonary artery and vein (Di Tullio et al., 1993). Therefore the false-positive TCD in our study may occur due to the above causes. The size of the foramen ovale was different from 0.5 mm to over 4 mm (Michaela et al., 1998). But in a case where the size of PFO was very small, air bubbles of the contrast solution could not passed through the right-to-left shunt in the small size of PFO even if the opening of foramen ovale was induced by increasing the thoracic pressure through Valsalva maneuver. So the embolic signal in TCD could not be detected (Bogousslavsky et al., 1996). These results coincided with our study of the false negative. In spite of this demerit, we think that a large scale studies about that the detection and therapy of PFO in the prevention of cryptogenic ischemic strokes should be conducted later on.

In our study, there was no statistical significance (P= 0.206) when we performed TEE and TCD test for PFO diagnosis. In the accuracy of PFO diagnosis based on TEE used as the gold standard, the sensitivity of PFO diagnosis was 90.9% which was regarded as being accurate.

Therefore the non-invasive TCD differed from the anti-invasive TEE because TCD is low in the cost, can evaluate conveniently the existence or nonexistence of a right to left shunt, and can screen the cerebrovascular disorder. And so we would like to recommend that TCD test in patients with a stroke is a useful and convenient method for the screening of the existence or nonexistence of a right to left shunt.

There is a restriction in our study because of the small number of the subjects. It was generally known that PFO

prevalence in young ages with cryptogenic ischemic stroke was higher than that in old ages with stroke (Silva et al., 2005). But we could not check the age spectrum in our study.

In the future, if large-scaled researches are performed, we will know whether a predictive factor for the diagnosis of PFO is age or not. We expect that PFO can be detected easily through TCD and can obtain more significantly clinical results for the prevention and therapy of PFO.

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