Pulsed Doppler Ultrasound of the Internal Carotid Artery for the Diagnosis of Patent Foramen Ovale in Patients with Ischemic Stroke

Short title: Carotid Ultrasound for the Diagnosis of PFO

Ayano Suzuki, MD[1],* Hidehiro Takekawa, MD, PhD[1], Keisuke Suzuki, MD, PhD[1], and Koichi Hirata MD, PhD[1]

[1]Department of Neurology, Dokkyo Medical University

*Corresponding author:
Ayano Suzuki, MD
Department of Neurology, Dokkyo Medical University,
880 Kitakobayashi, Mibu, Shimotsuga, Tochigi 321-0293, Japan
Tel: +81-282-86-1111; Fax: +81-282-86-5884
E-mail address: s.ayano.onigiri.0220@icloud.com

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Abstract

Purpose: The aim of this study was to assess the right-to-left shunts (RLs) associated with patent foramen ovale (PFO), which is essential for diagnosing paradoxical cerebral embolisms. Transesophageal echocardiography (TEE) and transcranial Doppler (TCD) are used for the detection of RLs. However, in some patients with comorbid diseases, such as cervical spondylosis and esophageal varices with cirrhosis, and in elderly women, TCD and TEE assessment are difficult. We compared the efficacy of carotid artery ultrasonography (C-US) and TEE in terms of the detection rate of PFO.

Methods: Fifty-eight consecutive patients with ischemic stroke (age: 57.0±19.0 years, 38 men and 20 women) were evaluated for PFO through TEE and C-US. In a TEE assessment, the diagnosis of PFO was made using the Valsalva maneuver with contrast agent injection. The internal carotid artery was evaluated with C-US. PFO was defined as the appearance of microembolic signals (MES) after release of Valsalva load with contrast agent injection.

Results: A PFO was detected in 30 patients. MES were observed in 25 patients using C-US. For the diagnosis of PFO, C-US had 83.3% sensitivity, 100% specificity, 100% positive predictive value, and 93.8% negative predictive value. In contrast, TEE had 53.3% sensitivity, 100% specificity, 100% positive predictive value, and 66.7% negative predictive value.

Conclusion: Our study suggests that C-US with Valsalva load release and contrast agent injection is beneficial for the diagnosis of PFO.

Introduction

Antithrombotic, antiplatelet, and anticoagulant agents are used in the secondary prevention of ischemic stroke, atherothrombotic brain infarction, and cardiogenic brain embolism, respectively[1]. In the absence of atrial fibrillation, the cause of cerebral embolism diagnosed by brain imaging is unclear in some patients. Such types of cerebral infarctions are known as embolic strokes of undetermined source (ESUS), and from the perspective of secondary prevention, the causes need to be determined[2].

Meanwhile, when a patent foramen ovale (PFO) associated with right-to-left shunts (RLs) or a pulmonary arteriovenous fistula (PAVF) is present, a thrombus may form in a deep vein of the lower extremities and flow into the cervical artery and may cause a paradoxical cerebral embolism[1]. Paradoxical cerebral embolism accounts for approximately 4% of the ESUS[3], and anticoagulant agents are used for its secondary prevention[1]. With this, diagnosing the presence of RLs is important in ischemic strokes.

Transesophageal echocardiography (TEE) is believed to be the most useful tool for the diagnosis of RLs[4]; however, the test is often difficult to perform on patients in the acute stage of cerebral infarction due to impaired consciousness and dysphagia. In addition, performing TEE in a patient with gastroesophageal varices could lead to a risk of bleeding[5]. For this reason, the diagnosis of RLs is often carried out using transcranial Doppler ultrasonography (TCD) and transcranial color flow imaging (TC-CFI) for the visualization of the middle cerebral artery (MCA) from the temporal bone[6][7]. However, these imaging methods may be affected by the patient's race and age[8], and using TCD and TC-CFI to monitor the blood flow in the MCA in elderly Japanese women is particularly difficult[9].

Moreover, carotid artery ultrasonography (C-US) is an indispensable and easy-to-perform tool for stroke patients and has been used for the diagnosis of a stenosis or obstruction of the cervical artery and ischemic stroke[10]. It allows visualization of the common carotid artery

(CCA) and internal carotid artery (ICA) in all stroke patients. Thus, if the diagnosis of RLs can be determined by examining the cervical artery, the test will be highly useful in clinical settings.

Therefore, we conducted a study on the use of C-US for diagnosing RLs using the ICA, which is directly linked to cerebral blood vessels, comparable or superior to TEE in terms of diagnostic yield in the detection of PFO.

Materials and methods

From a total of 2,393 patients who were diagnosed with ischemic stroke and admitted at the Department of Neurology of Dokkyo Medical University between October 2010 and March 2017, we studied 58 consecutive patients (age: 57.0±19.0 years, 38 men and 20 women) who were evaluated with both C-US and TEE.

The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) was used as the criteria for the classification of ischemic stroke[11)] and for the diagnosis of ESUS[2)]. Determination of the diagnosis of paradoxical cerebral embolism was performed in accordance with the Japan Academy of Neurosonology[12)]. In other words, cerebral embolism was considered due to the presence of RLs in the absence of other embolic sources. On the other hand, patients whose RLs could not be detected using C-US and TEE but were detected using TCD were diagnosed with PFO or PAVF based on the criteria established by the Japan Academy of Neurosonology[12)].

Diagnosis of RLs by C-US

C-US was performed within 3 days after the patients were diagnosed with ischemic stroke, and the diagnosis of RLs was determined within 7 days after the onset of the disease. The equipment used was the SSA-770A unit (Toshiba, Japan) with a sector-array probe (2.5 MHz). Ultrasound imaging was performed in a supine position with the head turned to the left and the neck extended. Pulsed Doppler ultrasound of the right ICA was performed in the region approximately 3.5 cm from the carotid bulb. The sample volume was made large enough to cover the blood vessel's diameter, and detection of RLs was carried out using the right ICA.

The presence or absence of RLs was determined on the basis of the diagnostic criteria using TCD[12], in which a contrast agent proposed by the Japan Academy of Neurosonology was used. A contrast agent was prepared by stirring 9 mL of a physiological saline solution and 1 mL of air with sufficient Valsalva load and injecting into the right intermediate basilic vein. Approximately 5 seconds later, the Valsalva load was released, and the right ICA was observed to check whether microbubbles of the contrast agent appeared as microembolic signals (MES) **(Fig. 1)**. The contrast agent was also administered intravenously without performing the Valsalva maneuver, and confirmation of the emergence of MES was carried out. The test was carried out 3 times, and RLs were considered present when MES were detected at least once. Moreover, the condition was diagnosed as PAVF in cases where MES were present even when the Valsalva maneuver was negative and was diagnosed as PFO in cases where MES were found only when the Valsalva maneuver was positive.

Diagnosis of RLs by TEE

TEE was performed by using the transesophageal multiplanar probe (2 to 7 MHz) of an iE33 Ultrasound System (Philips, Japan) under laryngopharyngeal local anesthesia and was carried out within 7 days after the diagnosis of RLs was determined based on the C-US.

The diagnosis of RLs was determined according to the criteria specified by the Japan Academy of Neurosonology[12]. Procedures were carried out using 1) Valsalva maneuver alone, 2) Valsalva maneuver and injection of contrast agent, and 3) injection of contrast agent alone. In procedure 2, the patient was diagnosed with RLs when the high-luminance granular ultrasound image of the right atrium appeared in the left atrium, and when its luminance was higher than that of the granular ultrasound image found in procedure 1. The patient was diagnosed with PFO when a high-luminance granular ultrasound image appeared within 3 cardiac beats after the release of the Valsalva load. In addition, the patient was diagnosed with PAVF or PFO when a high-luminance granular ultrasound image appeared in 4 cardiac beats or more and when a high-luminance granular ultrasound image was found in the left atrium. In procedures 2 and 3, when the high-luminance granular ultrasound image did not appear in the left atrium, the test was performed again, and a reconfirmation of the absence of RLs was carried out. The contrast agent was prepared by stirring 9 mL of physiological saline solution with 1 mL of air and was administered intravenously through the right intermediate basilic vein.

When a case was diagnosed as PFO, the classification was as follows: small shunt (1 to 5 high-luminance granular ultrasound images), medium shunt (6 to 25 high-luminance granular ultrasound images), and large shunt (more than 25 high-luminance granular ultrasound images)[12)].

Statistical analysis

To calculate the diagnostic yield of TEE and C-US in the detection of RLs, the following were determined: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy.

Ethical standard

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. The institutional review board of the Dokkyo Medical University Hospital approved the study (IRB approved number: R-2-8). All patients provided written informed consent to participate in the study.

Results

On the basis of the classification of cerebral infarctions, 21 patients were definitively diagnosed with paradoxical cerebral embolism, 5 with ESUS, and PFO was detected in 9 cases, but the definitive diagnosis could not be confirmed because of the presence of multiple causes such as cervical artery dissection and nonvalvular atrial fibrillation. **(Table 1)**.

The results of the diagnosis of PFO using the TEE and C-US are shown in **Table 2**. Among the 30 cases in which RLs could not be found based on the results of the TEE and C-US, 2 patients (a 75-year-old woman and a 37-year-old man) were diagnosed with RLs based on the TCD results. Therefore, RLs accounted for 30 cases (51.7%), all of which consisted of PFO.

The diagnostic yield in the diagnosis of PFO was examined, and the findings showed that TEE detected PFO in 16 cases with 53.3% sensitivity and 75.9% accuracy. On the contrary, C-US allowed for diagnosing 25 cases of PFO; the detection rate of PFO had 83.3% sensitivity and 91.4% accuracy, which were higher than those of TEE **(Table 3)**.

Using the TEE as a standard reference, findings showed that although the diagnostic yield of C-US had a sensitivity as high as 81.3% and a specificity of 71.4%; its PPV was as low as 52.0% while its NPV was as high as 90.9%. In addition, shunt types according to TEE were as follows: small shunts accounted for 3 cases, medium shunts for 6 cases, and large shunts for 7 cases. The C-US allowed for the diagnosis of PFO in all cases of small shunts. Among the 13 cases of medium shunts and large shunts, C-US did not detect PFO in 3 cases. When the 3 cases of small shunts were excluded and the diagnostic yield of C-US was determined using the TEE as a standard reference, findings showed a sensitivity of 76.9% and specificity of 71.4%, which showed the usefulness of C-US; however, the PPV was as low as 45.5% and the NPV was elevated as high 93.8% **(Table 4)**.

Discussion

In a study conducted on ischemic stroke patients, we examined the differences between using TEE and C-US in the determination of the diagnosis of RLs. As a result, our findings showed that all the participants had PFO and that C-US had a higher sensitivity, NPV, and accuracy compared to TEE; however, C-US might be more useful than TEE in the determination of the diagnosis of PFO. Likewise, if TEE was used as a standard reference for diagnosis, C-US showed a high NPV and if the diagnosis of PFO was not confirmed by C-US, the TEE findings were likely to yield the same result.

In the atrial septum formation, the orifice that remains present in the septum secundum is usually closed after birth because of an elevation of the left atrial pressure due to pulmonary circulation[13)]; however, if the hole does not close, the condition is known as a PFO. Its prevalence has been reported to range from 15% to 35% in healthy subjects[14)15)]. Meanwhile, approximately 30% of patients who develop ischemic stroke also have PFO[16)]. It is believed to be present in more than 40% of cryptogenic cerebral infarctions[6)]. As for ESUS, approximately 40% of the cases have been reported to have paradoxical cerebral embolisms mediated by PFO[3)]. Treatment aimed at eliminating the deep vein thrombosis for paradoxical cerebral embolisms due to PFO and PAVF is the secondary prevention of ischemic stroke; therefore, anticoagulant agents should be administered[1)]. Thus, accurately diagnosing paradoxical cerebral embolism is critical for treatment of secondary prevention.

TEE has been used up to this time for determining the diagnosis of RLs such as PFO. The diagnostic yield of TEE for those conditions has a sensitivity rate as high as 89.2% and a specificity rate as high as 91.4%[4)], but some cases have also been overlooked by TEE. On the other hand, TEE cannot be performed in some cases including in patients with poor general condition, such as those with impaired consciousness, and in patients undergoing combined treatments for gastroesophageal varices or other conditions. For such cases, evaluations of RLs have been carried out using other ultrasonographic studies.

Katsanos et al. [6)] previously carried out a systematic literature review of the diagnosis of PFO in patients with cryptogenic cerebral infarction. Their findings from 35 eligible studies including 3,067 patients have shown that the diagnostic yield of TCD in the determination of the diagnosis of PFO had a sensitivity of 96.1% and a specificity of 92.4%. However, for TEE, the specificity was 99.6% but the sensitivity was 45.1%. In addition, the area under the receiver operating curve was 0.86 for TEE and 0.98 for TCD, indicating that TCD was more useful. Furthermore, in a previous study conducted on 112 cases of ischemic stroke or transient ischemic attack, Komatsu et al.[7] attempted to diagnose RLs with contrast transcranial color-coded sonography of vertebral artery monitoring (cTCCS-VA) using a contrast agent. As a result, reported findings showed that in transcranial color-coded sonography (cTCCS) of the MCA from a temporal bone window, the diagnostic yield had a sensitivity of 84% and a specificity of 42%, whereas in the case of cTCCS-VA, the diagnostic yield had a sensitivity of 91% and a specificity of 40%, showing that cTCCS-VA had a higher sensitivity. Thus, TCD and cTCCS exhibited comparable or superior efficacy to that of TEE in determining the diagnosing of RLs.

Studies using the cervical artery for the diagnosis of RLs have also been reported. Censori B et al.[17] previously compared a method for performing TCD on the right MCA and a method using a second harmonic imaging duplex of the right CCA. Diagnosis of RLs was carried out on 100 patients, and the findings showed that the second harmonic imaging duplex of the right CCA had a sensitivity of 95.3%, a specificity of 100%, a PPV of 100%, and a NPV of 96.6% in patients who were diagnosed with large shunts on the basis of TCD results. This suggests that second harmonic imaging duplex can be useful as an alternative method if no adequate cranial bone window for TCD is found. It is impossible to assess the merits of this method in comparison with those of TEE because this is not a direct comparison with TEE. In a study conducted on 106 patients, Kobayashi et al.[18] identified the ICA from an orbital window by using the TCD and examined the use of the ICA for the diagnosis of RLs. They found that the rate of detection of RLs by the conventional TCD was 67% from the right MCA, 73% from the left MCA, and 80% from an orbital window. Also, a combined method using both MCA and ICA has been reported to achieve a detection rate of 100% rate for RLs. Our study was conducted using the ICA from an orbital window, and our findings suggested that, in terms of detection of RLs, using the ICA might be better than using the MCA.

In our study, we attempted to diagnose RLs by using the C-US, a method which was simpler than TCD, and as a result, our findings showed that, in the same way as with TCD, the RLs detection rate may be higher with C-US than with TEE. In addition, our study showed that the diagnostic yield of TEE in the determination of the diagnosis of PFO had a lower sensitivity and a lower NPV compared to that of C-US. TEE allows for confirmation of the direct filling of the contrast agent into right and left atrium. However, with the Valsalva maneuver, the blood flow may stagnate in the pulmonary artery and vein, and this may lead to rouleaux formation of erythrocytes. Observations indicate this to have low echogenicity compared to the echogenicity of the contrast agent, and this is diagnosed as non-smoke spontaneous individual contrast (NSSIC) [19]. However, NSSIC can be mistaken for RLs in some cases, and this may have been the cause of the low diagnostic yield of TEE.

TEE allows for estimation of the diameter of a PFO[12]. When a diagnosis using TEE was considered as the standard, the diagnostic yield of our method using the ICA showed a PPV of 52%. In addition, when only medium and large shunts were included in the study, the PPV was even lower. However, the results showed that the NPV was as high as 90%. This may have been due to the fact that cases of NSSIC which were misidentified as PFO during tests using TEE may have not been diagnosed as PFO when a method using the ICA was used. Furthermore, in medium and large shunts, the major flow of contrast agent may go mainly into the other arteries, such as the external carotid artery and the vertebral artery, and not into the ICA. However, because of the high PPV, the cases in which the diagnosis of PFO is considered negative in the tests using the ICA are also highly likely to be negative for PFO in the tests using the TEE.

There are a number of limitations to our study. The diagnostic criteria established by the Japan Academy of Neurosonology [12] were used, and all patients were diagnosed with PFO, but there may have been some patients with PAVF. In other words, prolonging the observation period may allow for detection of MES. In addition, we did not perform an analysis of the frequency of MES[20], and as a result, we cannot rule out the possibility that the patients diagnosed with PFO may also have shown MES due to other reasons such as the ulceration of plaques. Lastly, the diagnostic criteria for TCD [12] were used because there were no clearly defined diagnostic criteria for use with C-US; therefore, the possibility of PAVF among the patients diagnosed with PFO cannot be ruled out. This may have also been the reason for the variation in results from those of the diagnostic yield of TEE in the identification of PFO.

Conclusion

Our study has shown that the use of C-US for diagnosing RLs by using the ICA was comparable or superior to TEE in terms of diagnostic yield in the detection of PFO.

Conflicts of interest

There are no financial or other relations that could lead to a conflict of interest.

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Figure legend

Figure 1

Right-to-left shunts diagnosis by Pulsed Doppler Ultrasound of internal carotid artery

Pulsed Doppler ultrasound of right internal carotid artery was performed to diagnose the RLs (a). The Doppler waveform pattern of a patient without RLs is shown in “b”. If RLs are present, irregular high echoic signals called MES appears in the Pulsed Doppler waveform (c, white arrows).

C-US, carotid artery ultrasonography; ICA, internal carotid artery; MES, microembolic signals.

Table 1

Background characteristics of subjects

Age (years; median, range)	61.0 (18-82)
Male (n, %)	38 (65.5)
Large-artery atherosclerosis (n, %)	9 (15.5)
Small-artery occlusion (n, %)	4 (6.90)
Cardioembolism (n, %)	4 (6.90)
Paradoxical cerebral embolism (n, %)	21 (36.2)
Undetermined cause (PFO+) (n, %)	9 (15.5)
Undetermined cause (PFO-) (n, %)	6 (10.3)
ESUS (n, %)	5 (8.62)

PFO, patent foramen ovale; ESUS, embolic strokes of undetermined source

Table 2

Detection rate of patent foramen ovale

PFO detected using both TEE and C-US (n, %)	13 (22.4)
PFO detected using TEE only (n, %)	3 (5.17)
PFO detected using C-US only (n, %)	12 (20.7)
PFO not detected using both TEE and C-US (n, %)	30 (51.7)

PFO, patent foramen ovale; TEE, transesophageal echocardiography; C-US, carotid artery ultrasonography

Table 3

Diagnostic rate of patent foramen ovale

	Sensitivity	Specificity	PPV	NPV	Accuracy
TEE	53.3%	100%	100%	66.7%	75.9%
C-US	83.3%	100%	100%	84.8%	91.4%

PFO, patent foramen ovale; TEE, transesophageal echocardiography; PPV, Positive predictive value; NPV, negative predictive value

Table 4

Diagnostic rate of patent foramen ovale with carotid artery ultrasonography using transesophageal echocardiography as the standard reference

	Sensitivity	Specificity	PPV	NPV	Accuracy
All cases (n=58)	81.3%	71.4%	52.0%	90.9%	74.1%
Excluded small shunt (n=55)	76.9%	71.4%	45.5%	93.8%	72.7%

PPV, Positive predictive value; NPV, negative predictive value