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Detection of Right to Left Shunting Through a Patent Foramen Ovale in Japanese Patients with Ischemic Stroke by Transesophageal Echocardiography Using a Standardized Valsalva Maneuver

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We attempted to clarify the usefulness of transesophageal echocardiography performed using a standardized Valsalva maneuver to detect the presence of a patent foramen ovale in Japanese patients with ischemic stroke. Four hundred ninety six patients with ischemic stroke who were admitted to the Yokohama City Brain and Stroke Center between September 1999 and February 2002 were enrolled for the study. All the enrolled patients underwent transesophageal echocardiography with contrast injection and color Doppler imaging. During the procedure, a standardized Valsalva maneuver was performed to induce right to left shunting through a patent foramen ovale. Other related structural abnormalities, such as atrial septal aneurysm and the Chiari network anomaly, were also detected by the test. Transesophageal echocardiography without the Valsalva maneuver revealed a functional right to left communication in only 8.2% of the ischemic stroke patients, whereas the procedure conducted using a standardized Valsalva maneuver to provoke shunting revealed a patent foramen ovale in 15.3% of the patients. The presence of an atrial septal aneurysm or the Chiari network anomaly was not sensitive or specific enough to predict the presence of a patent foramen ovale as diagnosed by transesophageal echocardiography using the standardized Valsalva maneuver. Our results suggest that the standardized Valsalva maneuver is a safe and useful technique to detect the presence of a patent foramen ovale, which is potentially known to be associated with paradoxical embolism.

Key words: patent foramen ovale, ischemic stroke, Valsalva maneuver

INTRODUCTION

Even after extensive evaluation, the cause of ischemic stroke can be clarified in only about a half of the patients with ischemic stroke [1]. Recent investigations suggest the potential role of a functional right to left communication through a persistently patent foramen ovale in the development of paradoxical embolism, including that associated with ischemic stroke [2-6]. While the contribution of a patent foramen ovale in the onset of stroke remains speculative, its role may be strongly suspected when the onset of the stroke is associated with conditions causing elevation of the right atrial pressure, such as with diving, or in the case of young patients without evidence of progressive atherosclerosis [2-6]. On the other hand, autopsy studies have revealed that more than 25% of normal adult subjects show a potentially patent foramen ovale, the size tending to increase with age [7].

Transesophageal echocardiography, which enables us to visualize the left and

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right atria more clearly than transthoracic echocardiography, is a highly useful procedure for the detection of a patent foramen ovale. The reported incidence of patent foramen ovale varies from one report to another; ranging from 10% of the population [8] to more than 25% of the population [9]. Sensitive detection of a patent foramen ovale is crucial, even if it generates right to left shunting only under extreme conditions, such as during strong compression of the abdomen, because paradoxical embolism potentially causing ischemic stroke could occur under extremely unusual conditions, such as during diving [10], and it can now be prevented by appropriate medical or surgical treatment, including antithrombotic therapy [11], operative closure [12] or catheter-derived closure techniques [13-15].

In the present study, we tested the usefulness of abdominal compression during transesophageal echocardiography for detecting a patent foramen ovale that could not have been demonstrated by conventional transesophageal echocardiography with contrast injection. Since this study was conducted at a single institute, all the procedures, including abdominal compression, could be strictly standardized. We showed in this study that a patent foramen ovale could be detected in only less than a half of the cases without a maneuver to provoke the shunting. We also showed that the presence of other structural abnormalities known to be associated with a patent foramen ovale, such as an atrial septum aneurysm [16, 17] or the Chiari network anomaly [18], was neither sensitive nor specific enough to predict the presence of a patent foramen ovale. Our study results suggest that the incidence of patent foramen ovale in the Japanese population is similar to the previously published incidence of this condition in Caucasians [7].

METHODS

Patient Population

We enrolled 496 patients with ischemic stroke who were admitted to the Yokohama City Brain and Stroke Center between September 1999 and February 2002 for this study. The study was conducted in compliance with the Declaration of Helsinki, and informed consent was obtained from all of the enrolled patients prior to their participation in the study. Of the total, 155 patients were female and 341 were male. Thirty-three (33%) percent of the patients had a history of at least one episode of paroxysmal atrial fibrillation. More than 98% of the episodes of atrial fibrillation had been confirmed by 12-leads electrocardiography or ambulatory ECG. The mean age of the patients with a history of atrial fibrillation was 69 ± 9, which was significantly higher than the mean age of the patients who were in sinus rhythm, which was 60 ± 9 ($p = 0.0002$ by Student's unpaired t-test).

Detection of Patent Foramen Ovale by Transesophageal Echocardiography

All the enrolled patients underwent transthoracic as well as transesophageal echocardiography (Acuson Sequia512, Siemens, Germany), performed by experienced sonographers according to the following procedure. Transthoracic echocardiography was performed according to the clinical guidelines published by the American Heart Association [19]. Then, transesophageal echocardiography was performed under sedation of the patient by intravenous injection of flunitrazepam (2 mg). All the patients were initially screened for the presence of any structural abnormalities, such as valvular deformities, atrial septal aneurysm, or the Chiari network anomaly, using a 5-MHz multiplane transducer (TE-V5M) The presence of right to left shunting was examined by the injection of saline containing air-bubbles, according to a previously published procedure [19]. The standardized Valsalva maneuver, which was executed by hand compression of each patient's abdomen by the same technician using the same protocol, was applied in all patients to induce transient right to left shunting through a patent foramen ovale. The results were recorded on VHS videotapes for later evaluation.

The presence of right to left shunting was defined by the appearance of at least three microbubbles in the left atrium within three cardiac cycles after complete opacification of the right atrium. The diagnosis of atrial septal defect was established based on direct visualization of a septal defect by transesophageal echocardiography and the recording of turbulent left to right flow across the defect by color flow Doppler imaging.

Table 1 Right-to-Left Shunting Through a Patent Foramen Ovale Detected by Transesophageal Echocardiography with or without a Standardized Valsalva Maneuver.

	Sinus Rhythm (n =334)		Atrial Fibrillation (n =162)	
	PFO +	PFO −	PFO +	PFO −
Without VM	30	304	12	150
With VM	50	284	30	132

PFO+: Number of patients with right to left shunting as defined in the main text. PFO −: Number of patients in whom no right to left shunting was detected. VM: standardized Valsalva maneuver as described in the Methods section.

Other Structural Abnormalities Detected by Transesophageal Echocardiography

Other structural abnormalities that could potentially be associated with thromboembolism, such as an atrial septal aneurysm and the Chiari network anomaly, as well as left atrial thrombi, a well-known risk factor for thromboembolic events, were also diagnosed by transesophageal echocardiography, as follows; interatrial septal aneurysm was diagnosed when the atrial septum bulged 11 mm or more into one or the other atrium, or both [20]; Chiari network anomaly, a remnant of the septum spurium and the right valve of the sinus venosus, resulting from incomplete resorption of these structures, which is often associated with a patent foramen ovale, was diagnosed as the presence of striated abnormal echo shadow in the right atrium [21]; left atrial thrombi, detected as the presence of abnormal echo with specific characteristic, which were also diagnosed according to the criteria [22]. Since an atrial septal aneurysm [16, 17] and the Chiari network anomaly [18], which can be easily diagnosed by transesophageal echocardiography, have been described in a previous report to be frequently associated with the presence of a patent foramen ovale, we tested the predictive value of the presence of these structural abnormalities for the diagnosis of a patent foramen ovale.

Statistics

The numerical results were expressed as mean ± SD, unless otherwise specified. Differences between two groups of data were tested by the chi-square analysis, unless otherwise stated. A p value of less than 0.05 was considered to denote statistical significance.

RESULTS

Right to Left Communication through a Patent Foramen Ovale

Conventional transesophageal echocardiography performed without the Valsalva maneuver revealed functional right to left shunting in only 8.2% of the patients in this study (Table 1). In other words, right to left shunting through a patent foramen ovale was detected in only 12 of 162 patients with a history of atrial fibrillation and 30 of 334 patients with sinus rhythm, in the absence of any provocation of shunting. There was no significant difference in the rate of detection of shunting with a history of atrial fibrillation and that with sinus rhythm. With provocation of shunting by the standardized Valsalva maneuver, the percentage of detection of right to left shunting increased significantly from 8.2% to 15.3% ($p < 0.01$), that is, at least 18 of the 162 patients with a history of atrial fibrillation and 20 of the 334 patients with sinus rhythm had hidden right to left shunting through a patent foramen ovale, which was not evident without provocation by the Valsalva maneuver. The number of patients detected to have a patent foramen ovale increased significantly with provocation, both among patients with a history of atrial fibrillation ($p = 0.00027$) and among those with sinus rhythm ($p = 0.0021$).

Other Structural Abnormalities Detected by Transesophageal Echocardiography

More than 70% of patients with a history of atrial fibrillation had detectable left atrial thrombi. The number of patients detected to have structural abnormalities that may be potentially associated with thromboembolism, such as an atrial septal aneurysm or the

Table 2 Other Structural Abnormalities Detected by Transesophageal Echocardiography

	Sinus Rhythm	Atrial Fibrillation
ASA	70	11
Chiari	42	25
Total Number	334	162

ASA: Atrial septal aneurysm, Chiari: Chiari network anomaly.

Chiari network anomaly, is shown in Table 2. The presence of an atrial septal aneurysm predicted the presence of a patent foramen ovale, including those cases in which the right to left shunting could be detected only after provocation, with a sensitivity and specificity of 0.53 and 0.48. The sensitivity and specificity of prediction were even lower when the presence of the Chiari network anomaly was used as the predictor. The accuracy of the prediction based on the presence of an atrial septal aneurysm and the Chiari network anomaly was 0.33, and 0.44, respectively.

DISCUSSION

We have shown here that conventional transesophageal echocardiography with contrast injection and color Doppler flow imaging allowed the detection of a patent foramen ovale in only less than a half of the cases. Our results also demonstrated that the predictive value of presence of structural abnormalities known to be associated with a patent foramen ovale, such as atrial septal aneurysm [16, 17] or the Chiari network anomaly [18], is neither specific nor sensitive enough for accurate prediction of the presence of a patent foramen ovale. Our study results suggest that provocation of right to left shunting by an appropriate method, such as a standardized Valsalva maneuver, during transesophageal echocardiography, is probably the most appropriate method for the detection of a patent foramen ovale, which can be a potential cause of paradoxical embolism.

To date, there are no autopsy-based reports of the incidence of patent foramen ovale in Japanese patients. If it can be assumed that the incidence of a patent foramen ovale in the Japanese population is similar to that reported previously for Caucasians [7], our results would suggest that even by transesophageal echocardiography conducted with provocation of right to left shunting, a patent foramen ovale can be detected in only 60% of the patients. Nevertheless, the true sensitivity and specificity of our method cannot be estimated without a precise knowledge of the anatomic incidence of patent foramen ovale in the Japanese population. Indeed, a previous study suggested that the incidence of patent foramen ovale may be influenced by the racial origin of a population [23]. On the other hand, we speculate that a functional patent foramen ovale with right to left shunting as demonstrated by the method described in our study might be a more appropriate indication for treatment than pathologically or anatomically defined patent foramen ovale, because not all of the cases with an anatomically defined patent foramen ovale show right to left shunting which is potentially associated with paradoxical embolism.

While we included only patients with ischemic stroke in this study, it was difficult for us to identify the cause of the stroke in all the cases. Indeed, most of the patients were old enough to have atherosclerotic plaques, which can cause not only atherothrombotic stroke, but also so-called lacunar infarction. Moreover, it would be reasonable to suppose that most of the patients might have had episodic arrhythmia, which can be a cause of cardiogenic emboli, regardless of whether or not the arrhythmia can be clinically documented. In fact, there were no patients specifically suspected to have paradoxical embolism among our enrolled cases. However, we must also emphasize here that the possible contribution of paradoxical emboli cannot be completely excluded in any of the cases, especially in those with concealed right to left shunting through a patent foramen ovale. These patients might have benefits from medical or surgical treatment. Indeed, there are many studies that have demonstrated the

preventive effects of anticoagulants against ischemic stroke. Although many investigators believe that these preventive effects are attributable to the prevention of thrombus formation in the left atrium or in the arterial circulation, there is still the possibility that certain percentage of the patients might derive the benefits of such treatment from the prevention of venous thrombosis and paradoxical embolism. In a group of patients selected based on a strong suspicion of paradoxical embolism, obvious benefits of closure of a patent foramen ovale, either by the transcatheter technique [13, 24] or by surgical closure, have been reported [25, 26]. Recent progress in the trascatheter tecnnique [27] might allow future clinical studies to demonstrate the exact role of right to left shunting in the onset of ischemic stroke of unknown cause, and the true importance of accurate detection of potential right to left shunting through a patent foramen ovale can then be clarified.

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REFERENCE

1) Hart RG, Miller VT. Cerebral infarction in young adults: a practical approach. Stroke 14: 110-114, 1983
2) Lechat P, Mas JL, Lascault G, Loron P, Theard M, Klimczac M, Drobinski G, Thomas D, Grosgogeat Y. Prevalence of patent foramen ovale in patients with stroke. N Engl J Med 318: 1148-1152, 1988
3) Cabanes L, Mas JL, Cohen A, Amarenco P, Cabanes PA, Oubary P, Chedru F, Guerin F, Bousser MG, de Recondo J. Atrial septal aneurysm and patent foramen ovale as risk factors for cryptogenic stroke in patients less than 55 years of age. A study using transesophageal echocardiography. Stroke 24: 1865-1873, 1993
4) Di Tullio M, Sacco RL, Gopal A, Mohr JP, Homma S. Patent foramen ovale as a risk factor for cryptogenic stroke. Ann Intern Med 117: 461-465, 1992
5) Webster MW, Chancellor AM, Smith HJ, Swift DL, Sharpe DN, Bass NM, Glasgow GL, Patent foramen ovale in young stroke patients. Lancet 2: 11-12, 1988
6) Wu LA, Malouf JF, Dearani JA, Hagler DJ, Reeder GS, Petty GW, Khandheria BK. Patent foramen ovale in cryptogenic stroke: current understanding and management options. Arch Intern Med 164: 950-956, 2004
7) Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc 59: 17-20, 1984
8) Fisher DC, Fisher EA, Budd JH, Rosen SE, Goldman ME, The incidence of patent foramen ovale in 1,000 consecutive patients. A contrast transesophageal echocardiography study. Chest 107: 1504-1509, 1995
9) Meissner I, Whisnant JP, Khandheria BK, Spittell PC, O'Fallon WM, Pascoe RD, Enriquez-Sarano M, Seward JB, Covalt JL, Sicks JD, Wiebers DO. Prevalence of potential risk factors for stroke assessed by transesophageal echocardiography and carotid ultrasonography: the SPARC study. Stroke Prevention: Assessment of Risk in a Community. Mayo Clin Proc 74: 862-869, 1999
10) Schwerzmann M, Seiler C, Lipp E, Guzman R, Lovblad KO, Kraus M, Kucher N. Relation between directly detected patent foramen ovale and ischemic brain lesions in sport divers. Ann Intern Med 134: 21-24, 2001
11) Bogousslavsky J, Garazi S, Jeanrenaud X, Aebischer N, Van Melle G. Stroke recurrence in patients with patent foramen ovale: the Lausanne Study. Lausanne Stroke with Paradoxal Embolism Study Group. Neurology 46: 1301-1305, 1996
12) Orgera MA, O'Malley PG, Taylor AJ. Secondary prevention of cerebral ischemia in patent foramen ovale: systematic review and meta-analysis. South Med J 94: 699-703, 2001
13) Khairy P, O'Donnell CP, Landzberg MJ. Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli: a systematic review. Ann Intern Med 139: 753-760, 2003
14) Bridges ND, Hellenbrand W, Latson L, Filiano J, Newburger JW, Lock JE. Transcatheter closure of patent foramen ovale after presumed paradoxical embolism. Circulation 86: 1902-1908, 1992
15) Martin F, Sanchez PL, Doherty E, Colon-Hernandez PJ, Delgado G, Inglessis I, Scott N, Hung J, King ME, Buonanno F, Demirjian Z, de Moor M, Palacios IF. Percutaneous transcatheter closure of patent foramen ovale in patients with paradoxical embolism. Circulation 106: 1121-1126, 2002
16) Pearson AC, Nagelhout D, Castello R, Gomez CR, Labovitz AJ. Atrial septal aneurysm and stroke: a transesophageal echocardiographic study. J Am Coll Cardiol 18: 1223-1229, 1991
17) Mugge A, Daniel WG, Angermann C, Spes C, Khandheria BK, Kronzon I, Freedberg RS, Keren A, Denning K, Engberding R, *et al*. Atrial septal aneurysm in adult patients. A multicenter study using transthoracic and transesophageal echocardiography.

Circulation 91: 2785-2792, 1995
18) Kerut EK, Norfleet WT, Plotnick GD, Giles TD, Patent foramen ovale: a review of associated conditions and the impact of physiological size. J Am Coll Cardiol 38: 613-623, 2001
19) Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, Douglas PS, Faxon DP, Gillam LD, Kimball TR, Kussmaul WG, Pearlman AS, Philbrick JT, Rakowski H, Thys DM, Antman EM, Smith SC, Jr., Alpert JS, Gregoratos G, Anderson JL, Hiratzka LF, Hunt SA, Fuster V, Jacobs AK, Gibbons RJ, Russell RO. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). Circulation 108: 1146-1162, 2003
20) Mas JL, Arquizan C, Lamy C, Zuber M, Cabanes L, Derumeaux G, Coste J. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. N Engl J Med 345: 1740-1746, 2001
21) Schneider B, Hofmann T, Justen MH, Meinertz T.Chiari's network: normal anatomic variant or risk factor for arterial embolic events? J Am Coll Cardiol 26: 203-210, 1995
22) Klein AL, Grimm RA, Murray RD, Apperson-Hansen C, Asinger RW, Black IW, Davidoff R, Erbel R, Halperin JL, Orsinelli DA, Porter TR, Stoddard MF. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. N Engl J Med 344: 1411-1420, 2001
23) Rokicki W, Leung M, Kohut J, Durmala J, Borowicka E. Population dependent differences of distribution of congenital heart malformations. Wiad Lek 56: 34-39, 2003
24) Wahl A, Meier B, Haxel B, Nedeltchev K, Arnold M, Eicher E, Sturzenegger M, Seiler C, Mattle HP, Windecker S. Prognosis after percutaneous closure of patent foramen ovale for paradoxical embolism. Neurology 57: 1330-1332, 2001
25) Devuyst G, Bogousslavsky J, Ruchat P, Jeanrenaud X, Despland PA, Regli F, Aebischer N, Karpuz HM, Castillo V, Guffi M, Sadeghi H. Prognosis after stroke followed by surgical closure of patent foramen ovale: a prospective follow-up study with brain MRI and simultaneous transesophageal and transcranial Doppler ultrasound. Neurology 47: 1162-1166, 1996
26) Homma S, Di Tullio MR, Sacco RL, Sciacca RR, Smith C, Mohr JP. Surgical closure of patent foramen ovale in cryptogenic stroke patients. Stroke 28: 2376-2381, 1997
27) Schwerzmann M, Windecker S, Wahl A, Mehta H, Nedeltchev K, Mattle H, Seiler C, Meier B. Percutaneous closure of patent foramen ovale: impact of device design on safety and efficacy. Heart 90: 186-190, 2004