Transesophageal Echocardiographic Detection of Cardiac Sources of Embolism in Elderly Patients with Ischemic Stroke

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Objective The aim of this study was to clarify the role of transesophageal echocardiography in detecting cardiac sources of embolism in elderly stroke patients. **Methods** We performed transesophageal echocardiography in 77 patients ≥ 70 years old (mean 76.9) with ischemic stroke and investigated embolic sources. Thirty-seven patients were in sinus rhythm (SR) and 40 in atrial fibrillation (Af). **Results** Left atrial spontaneous echo contrast was detected in 73% of Af and in 14% of SR ($p < 0.01$). Left atrial thrombus was present in 10% of Af and none of SR ($p < 0.05$). Patent foramen ovale, atrial septal aneurysm, and aortic atherosclerotic plaque ≥ 4.0 mm in thickness in the proximal aortic arch were more commonly found in patients with SR. **Conclusions** In elderly ischemic stroke patients, 1) Left atrial spontaneous echo contrast and thrombus are more commonly detected in patients with Af, reflecting left atrial enlargement and blood stasis, and 2) atrial septal aneurysm, patent foramen ovale and aortic atherosclerotic plaque ≥ 4.0 mm in thickness in the proximal aortic arch are important findings in patients with SR.

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Key words: cerebral embolism, embolic source, diagnosis

Introduction

Recently, hemorrhagic stroke has remarkably decreased in Japan. However, the prevalence of ischemic stroke has shown a rather gradual decrease. Furthermore, the morbidity and mortality of ischemic stroke is still high and has increased with advancing age (1, 2). Therefore, it is still a major concern for us to determine how to prevent and manage elderly patients with ischemic stroke.

embolic source in an elderly patient with ischemic stroke. Therefore, we designed this study to characterize the sources of embolism in elderly ischemic stroke patients with both sinus rhythm and atrial fibrillation and to clarify the role of transesophageal echocardiographic examination in elderly patients.

Subjects and Methods

Between June 1995 and September 1997, we recruited patients older than age 70 years with “completed ischemic stroke” referred to the echocardiography laboratory of Kobe Rehabilitation Hospital for a transesophageal echocardiographic examination. The study group consisted of 77 consecutive patients (47 men and 30 women, age ranged 70 to 90 years, mean 76.9 ± 4.4 years). Thirty-seven patients were in sinus rhythm (SR) and 40 in atrial fibrillation (Af).

All patients underwent computed tomography (CT) imaging before echocardiographic examination to confirm the diagnosis of completed ischemic stroke. A completed ischemic stroke was defined as rapidly developing clinical signs of focal disturbance of cerebral function lasting longer than 24 hours

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Previous reports suggest that 6–39% of ischemic stroke are caused by cardiogenic emboli (3–8). Left atrial spontaneous echo contrast and thrombus formation associated with atrial fibrillation have been reported as one of the most important cardiac sources of embolism (9–13). Using transesophageal echocardiography, other possible sources of embolism including atrial septal aneurysm (14–19), patent foramen ovale (18, 20–27) and aortic atherosclerotic plaque (28–40) have been reported as independent risk factors of ischemic stroke. However, previous studies have not shown characteristics of an

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with no apparent cause other than that of vascular origin, while CT showed an area of low attenuation compatible with the clinical signs and symptoms.

Transthoracic and transesophageal echocardiography with contrast study were performed. M-mode, two-dimensional and Doppler echocardiographic studies were performed with the patients in the left lateral decubitus position using a commercially available echocardiographic machine (Toshiba, SSH-160A, Tokyo) with 3.5- and 2.5-MHz phased-array transducer. All echo images were recorded on 0.5-in. (1.27-cm) SVHS video tape for subsequent analysis. Standard views including parasternal, apical and subcostal views were obtained in all patients.

Figure 1. Transesophageal echocardiographic image demonstrating left atrial spontaneous echo contrast defined as “smoke-life” echoes swirling slowly in the left atrium. Ao: aorta, LA: left atrium, LAA: left atrial appendage.

Figure 2. Transesophageal echocardiographic images of oscillating atrial septal aneurysm (arrow). LA: left atrium, RA: right atrium, RV: right ventricle.

Transesophageal echocardiography was performed with a biplane 5-MHz phased array probe. The echocardiographic images were recorded on SVHS video tape for later analysis. After routine transesophageal echocardiographic examination of embolic sources, contrast echocardiography with saline injection during the Valsalva maneuver was also performed as previously reported (26). The following possible sources of embolism were investigated: 1) left atrial or left atrial append-

Figure 3. Transesophageal echocardiographic images of patent foramen ovale with right-to-left shunts. After intravenous injection of hand agitated saline, microcavitations appear in the left atrium during Valsalva maneuver (arrows). LA: left atrium, RA: right atrium.

Figure 4. Transesophageal echocardiographic image of protruding atherosclerotic plaque in the aorta (arrows). Ao: aorta.

age thrombus, 2) left atrial spontaneous echo contrast (defined as "smoke-like" echoes swirling slowly in the left atrium) (Fig. 1), 3) atrial septal aneurysm (defined as a protrusion of the aneurysm >10 mm beyond the plane of the atrial septum into either the right or left atrium according to the published criteria (19) (Fig. 2), 4) patent foramen ovale (defined using contrast echocardiography based on the appearance of more than five microcavitations after the Valsalva maneuver into the left atrium within three cardiac cycle after intravenous injection of hand agitated saline) (Fig. 3), 5) left ventricular thrombus, 6) left atrial or ventricular tumor, 7) aortic or mitral valvular myxomatous thickening or vegetation, 8) aortic atherosclerotic plaque (AoP) ≥ 4.0 mm in thickness in the proximal aortic arch (Fig. 4). Left atrial diameter (LAD) measured by transthoracic echocardiography, and left atrial appendage flow velocity measured by transesophageal echocardiography were also analyzed. The carotid artery stenosis $\geq 70\%$ was defined by either angiography, carotid echo or magnetic resonance angiography.

Statistical analysis

We used the chi-square test or Fisher's exact test for categorical variables to test significance of differences between two groups of patients. We used unpaired t test to compare the left atrial diameter and left atrial appendage flow velocity between two groups. A level of $p < 0.05$ was considered to be statistically significant.

Results

Transesophageal echocardiography was safely performed in all patients. Clinical characteristics of the study patients are shown in Table 1. There were no differences in the prevalence of diabetes mellitus (group SR: 19% vs group Af: 23%, $p = 0.699$) and cigarette smoking (group SR: 30% vs group Af: 25%, $p = 0.471$) between the two groups. However, hypertension (group SR: 65% vs group Af: 43%, $p < 0.05$) and hyperlipidemia (group SR: 49% vs group Af: 25%, $p < 0.05$) were more common in patients with SR compared with Af. Total

cholesterol levels were significantly higher in patients with sinus rhythm (group SR: 204.1 ± 34.0 vs group Af: 179.1 ± 35.6 mg/dl, $p < 0.01$). Serum triglyceride (group SR: 126.1 ± 45.6 vs group Af: 109.7 ± 48.3 mg/dl, $p = 0.150$) and HDL-cholesterol levels (group SR: 42.2 ± 9.7 vs group Af: 45.9 ± 12.7 mg/dl, $p = 0.177$) were not different between the two groups. In group Af, LAD measured by transthoracic M-mode echocardiography was significantly larger (group Af: 4.1 ± 0.9 vs group SR: 3.3 ± 0.7 cm, $p < 0.01$) and left atrial appendage flow velocity was significantly lower (group Af: 33 ± 21 vs group SR: 64 ± 27 cm/sec, $p < 0.01$) compared with group SR, respectively (Table 2).

The prevalences of the cardiac and vascular sources of embolism diagnosed by transthoracic and transesophageal echocardiography are shown in Table 2. Transthoracic echocardiography demonstrated cardiac abnormalities in 12 of 40 (30%) patients with Af and in 14 of 37 (38%) patients with SR. In 70 of 77 patients (91%), transesophageal echocardiography revealed the following additional findings.

Left atrial spontaneous echo contrast was detected in 29 of 40 (73%) patients with Af and 5 of 37 (14%) patients with SR ($p < 0.01$). Left atrial thrombus was present in 4 of 40 (10%) patients with Af and none of SR ($p < 0.05$). Patent foramen ovale was detected in 13 of 37 (35%) patients with SR and 3 of 40 (8%) patients with Af ($p < 0.01$). Atrial septal aneurysm was found in 3 of 40 patients (8%) with Af and 10 of 37 patients (27%) with SR ($p < 0.05$). Aortic atherosclerotic plaque ≥ 4.0 mm in thickness in the proximal aortic arch was found in 16 of 40 (40%) patients with Af and 25 of 37 (68%) patients with SR ($p < 0.05$). Left ventricular thrombus, intracardiac tumor, or valvular masses were not detected in this study population.

Discussion

The present study demonstrates that in elderly patients with ischemic stroke transesophageal echocardiography reveals cardiac and vascular sources of embolism in majority of patients with both Af and SR. In patients with Af, left atrial spontaneous echo contrast and left atrial thrombus were more common

Table 1. Clinical Characteristics

		Group Af (n=40)	Group SR (n=37)	p value
Age (years)		75.8 ± 4.8	78.1 ± 3.7	< 0.05
BMI (kg/m^2)		20.7 ± 3.1	21.4 ± 2.5	0.269
Smoking	-no. (%)	10 (25%)	12 (30%)	0.471
Hypertension	-no. (%)	17 (43%)	24 (65%)	< 0.05
Diabetes mellitus	-no. (%)	9 (23%)	7 (19%)	0.699
Hyperlipidemia	-no. (%)	10 (25%)	18 (49%)	< 0.05
Carotid stenosis ($\geq 70\%$)	-no. (%)	3 (8%)	7 (19%)	0.121
Total cholesterol (mg/dl)		179.1 ± 35.6	204.1 ± 34.0	< 0.01
HDL-cholesterol (mg/dl)		45.9 ± 12.7	42.2 ± 9.7	0.177
Triglyceride (mg/dl)		109.7 ± 48.3	126.1 ± 45.6	0.150

Af: atrial fibrillation, SR: sinus rhythm, BMI: body mass index.

Table 2. Transthoracic and Transesophageal Echocardiography Findings

		Group Af (n=40)	Group SR (n=37)	p value
Transthoracic echocardiography				
Valvular heart diseases	-no.(%)	8 (20%)	6 (16%)	0.667
Myocardial infarction	-no.(%)	3 (8%)	5 (14%)	0.388
Others	-no.(%)	1 (3%)	3 (8%)	0.268
LAD (cm)		4.1±0.9	3.3±0.7	<0.01
Transesophageal echocardiography				
LASEC	-no.(%)	29 (73%)	5 (14%)	<0.01
LATH	-no.(%)	4 (10%)	0 (0%)	<0.05
PFO	-no.(%)	3 (8%)	13 (35%)	<0.01
ASA	-no.(%)	3 (8%)	10 (27%)	<0.05
AoP (≥4.0 mm)	-no.(%)	16 (40%)	25 (68%)	<0.05
LAA flow velocity (cm/sec)		33±21	64±27	<0.01

Af: atrial fibrillation, SR: sinus rhythm, LAD: left atrial diameter, LASEC: left atrial spontaneous echo contrast, LATH: left atrial thrombus, PFO: patent foramen ovale, ASA: atrial septal aneurysm, AoP: atherosclerotic plaque in the proximal aortic arch, LAA: left atrial appendage.

findings. On the other hand, atrial septal aneurysm, patent foramen ovale and atherosclerotic plaque in the proximal aortic arch were more frequently detected in patients with SR.

Previous studies with transesophageal echocardiography

Previous reports that compared transthoracic and transesophageal echocardiography in patients with stroke and transient ischemic attack showed the superiority of transesophageal echocardiography in detecting cardiac sources of embolism (41–51). Pop et al (42) studied 72 patients with transient ischemic attack or non-disabling stroke. They reported that transesophageal echocardiography defined morphologic abnormalities in 5 (9%) of 53 patients without cardiac abnormalities on clinical examination and in 6 (32%) of 19 patients with one or more clinical cardiac abnormalities. They also reported that in 32 (44%) of 72 patients transesophageal echocardiography identified thoracic aortic atherosclerotic plaques. However, in their study, the prevalence of atrial septal aneurysm or patent foramen ovale was uncertain.

On the other hand, Lee et al reported that transesophageal echocardiography demonstrated at least one intracardiac abnormality, such as a left atrial or left atrial appendage thrombus, a patent foramen ovale, spontaneous echo contrast, and mitral valve strands in 26 (52%) of 50 patients with a negative transthoracic echocardiogram for potential sources of emboli (44). Similarly, Rauh et al demonstrated that transesophageal echocardiography revealed left atrial appendage thrombus in 3, atrial septal aneurysm in 2, patent foramen ovale in 7, and aortic plaque in 19 of 30 ischemic stroke patients with SR and normal transthoracic echocardiography and without carotid artery stenosis (46). In addition, they and other investigators have shown the utility of transesophageal echocardiography in therapeutic stratification of ischemic stroke patients (46, 48). Our results are consistent with these previous reports.

Left atrial spontaneous echo contrast and thrombus

Af with or without valvular heart diseases has been known as an important risk factor of ischemic stroke (5, 7, 52–55). Af is reported to present in up to 24% of all ischemic stroke and in almost half of cardioembolic stroke (7). Left atrial blood stasis represented by left atrial dilatation, the presence of left atrial spontaneous echo contrast and decreased left atrial appendage function have been reported to be associated with left atrial thrombus formation (10–13, 56). In the present study, we observed a larger left atrial dimension, a higher prevalence of the left atrial spontaneous echo contrast and a lower left atrial appendage flow velocity in elderly stroke patients with Af compared with those in SR. Interestingly, some authors reported that up to one-third of Af findings in ischemic stroke cases are coincidental (57). Our finding that sources of embolism not related to Af were detected in about 50% of patients with Af may support their observation.

Atrial septal aneurysm and patent foramen ovale

Patent foramen ovale was found in 27 to 35% of autopsy series (58, 59). However, using transthoracic or transesophageal contrast echocardiography, patent foramen ovale has been reported to be present in only 3.2 to 22% (average: 12%) of normal subjects (18, 20–26). The reason for the lower prevalence of patent foramen ovale compared with autopsy series is uncertain. Lechat et al speculated that left atrial pressure may remain higher than the right atrial pressure after Valsalva maneuver in some patent foramen ovale cases (20). Webster et al suggested that half of these patent foramen ovale cases in autopsy series were too small to be detected by contrast method (21). Early studies using transthoracic contrast echocardiography described a high incidence of patent foramen ovale in young stroke patients compared with control subjects (20, 21). Although the prevalence was not as high as in the younger

patients, patent foramen ovale has been detected in all age groups more often than in the control group (22, 23, 26). However in the very elderly patients group, the significance of patent foramen ovale as a possible source of emboli has not been clarified. We found that the overall prevalence of patent foramen ovale in the current study was similar to that previously reported in all age groups and the prevalence was higher in patients with SR (37%) than in patients with Af (11%).

Atrial septal aneurysm with or without patent foramen ovale has also been considered as an independent risk factor of arterial embolism, although the mechanism of thrombus formation has not been clarified (14–19). Meta-analysis of published transesophageal echocardiography studies demonstrated that the frequency of atrial septal aneurysm was on average 8.8% of patients with cerebral and/or peripheral embolism (60). The prevalence and significance of atrial septal aneurysm as well as patent foramen ovale in elderly stroke patients remain uncertain. In the present study, atrial septal aneurysm was detected at the same or at a higher frequency in elderly stroke patients with SR than can be expected from previous studies including whole age groups.

These results suggest that atrial septal aneurysm and patent foramen ovale may play some role as possible sources of embolism in elderly patients with sinus rhythm and should be investigated as well as in younger patients.

Aortic atherosclerotic plaque

We also showed a high incidence of atherosclerotic plaque in the aortic arch both in patients with SR and Af. Recently, atherosclerotic plaque in the aorta has become easily visualized using transesophageal echocardiography. Several investigators have reported a strong association between atherosclerotic plaque of the aorta and ischemic stroke (28–40). Karalis and coworkers found intraaortic atherosclerotic debris (plaque) in 38 (7%) of 556 patients undergoing transesophageal echocardiography (28). They observed an embolic event in 11 (31%) of 36 study patients with intraaortic atherosclerotic debris. Tunick et al compared 122 stroke patients with control subjects (29). They found that the presence of protruding atheromas in the thoracic aorta was strongly related to the occurrence of embolic symptoms. Amarenco et al also reported that atherosclerotic plaques ≥ 4 mm in the ascending or proximal aortic arch were found in 36 (14.4%) of 250 patients with stroke but in only 5 (2%) of 250 control subjects (34). They concluded that atherosclerotic disease of the aortic arch should be considered as a risk factor and a possible source of embolism for ischemic stroke. The same investigators recently reported that stroke patients with atherosclerotic plaque ≥ 4 mm in the ascending or proximal aortic arch had a higher incidence (11.9 per 100 person-years) of recurrent brain infarction as compared with 3.5 person-years in patients with a wall thickness of 1 to 3.9 mm and 2.8 per 100 person-years in patients with a wall thickness of < 1 mm (40). In the current study, we found a higher incidence of atherosclerotic plaques ≥ 4 mm in the ascending aorta or proximal aortic arch especially in patients with SR. Furthermore, transesophageal echocardiography detected other

possible cardiac sources of embolism, such as atrial septal aneurysm and patent foramen ovale, in 12 (48%) of 25 patients with aortic atherosclerotic plaque in group SR and in 2 (13%) of 16 patients in group Af. It is still not clear whether the coexistence of aortic atherosclerotic plaque in the aortic arch and other cardiac sources of embolism causes a higher risk for ischemic stroke. Future follow up studies with large numbers of patients are necessary to answer this question.

The present study has several limitations. First, we investigated a relatively small number of patients in each group without a normal control group. However, it is ethically difficult to examine apparently normal subjects age ≥ 70 . Even if we had served other elderly patients with various cardiac diseases referred to transesophageal echocardiographic examination as a control, it would not have been the true control group. Secondly, although transesophageal echocardiographic examination altered the therapy in some patients with Af, the impact of transesophageal echocardiography on the therapeutic strategies in stroke patients with SR is still unknown. Ongoing controlled prospective studies will clarify the role of anticoagulation, antiplatelet therapy, or surgical intervention in patients with atrial septal aneurysm, patent foramen ovale or atherosclerotic plaque. Finally, since this is a retrospective, single center study, a prospective study with larger numbers may be necessary to confirm our preliminary observation.

In conclusion, transesophageal echocardiography demonstrates various cardiac or vascular sources of embolism in elderly patients with ischemic stroke as it does in younger patients. Left atrial spontaneous echo contrast or thrombus is a more common finding in patients with Af. On the other hand, atrial septal aneurysm, patent foramen ovale and aortic atherosclerotic plaque ≥ 4.0 mm in thickness in the proximal aortic arch were more frequently detected in patients with SR. Whether the presence of multiple embolic sources may increase the risk of stroke and some therapeutic strategies including anticoagulation, antiplatelets, and surgical approaches can improve their prognosis remains to be studied.

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