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Difference Among Embolic Sources Between Younger and Older Patients with Stroke of Undetermined Source on Routine Diagnostic Assessment Including Transesophageal Echocardiography

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Abstract

Background: The distribution of embolic sources in patients with embolic stroke of undetermined source (ESUS) remains unclear. Furthermore, the difference among embolic sources according to age is unknown. The aim of this study was to identify the distribution of embolic sources in younger and older patients with embolic strokes who underwent routine diagnostic assessment with transesophageal echocardiography (TEE) and to evaluate the distribution of paradoxical embolism related to patent foramen ovale (PFO) between younger and older.

Methods and Results: Between May 2012 and December 2017, 102 ESUS patients underwent routine diagnostic assessment including TEE at our hospital to identify the specific cause of their embolic stroke. We compared the causes of embolic stroke between younger (<60 years; mean age, 49.3 ± 10.9 years; n=24) and older (>60 years; mean age, 74.8 ± 6.2 years; n=78) patients. Older patients had significantly higher rates of aortic arch atherosclerotic plaques (4.2% vs. 48.7%; p <0.001). The other causes were not significantly different between the two groups. Especially in paradoxical embolism related to PFO, younger patients had fewer other embolic sources in addition to PFO or both PFO and atrial septal aneurysm (ASA) than older patients. However, older patients also exhibited PFO or both PFO and ASA (32.6%) without other embolic sources.

Conclusions: Our study suggests that embolic source of ESUS to undergo routine diagnostic assessment including transesophageal echocardiography (TEE) is similar between younger and older. However, the total numbers of embolic sources is significantly higher in older patients. In paradoxical embolism related to PFO, 33% of older patients had no other identifiable cause of embolic stroke besides a PFO.

Key Words

Embolic stroke of undetermined source • Age • Patent foramen ovale

Introduction

Embolic stroke of undetermined source (ESUS) is a form of stroke defined based on a set of criteria proposed by the Cryptogenic Strokes/ESUS International Working Group [1]. Although the causes of ESUS have been previously reported in multiple studies, the cause of stroke could not be identified using the ESUS criteria in a number of patients. Moreover, this

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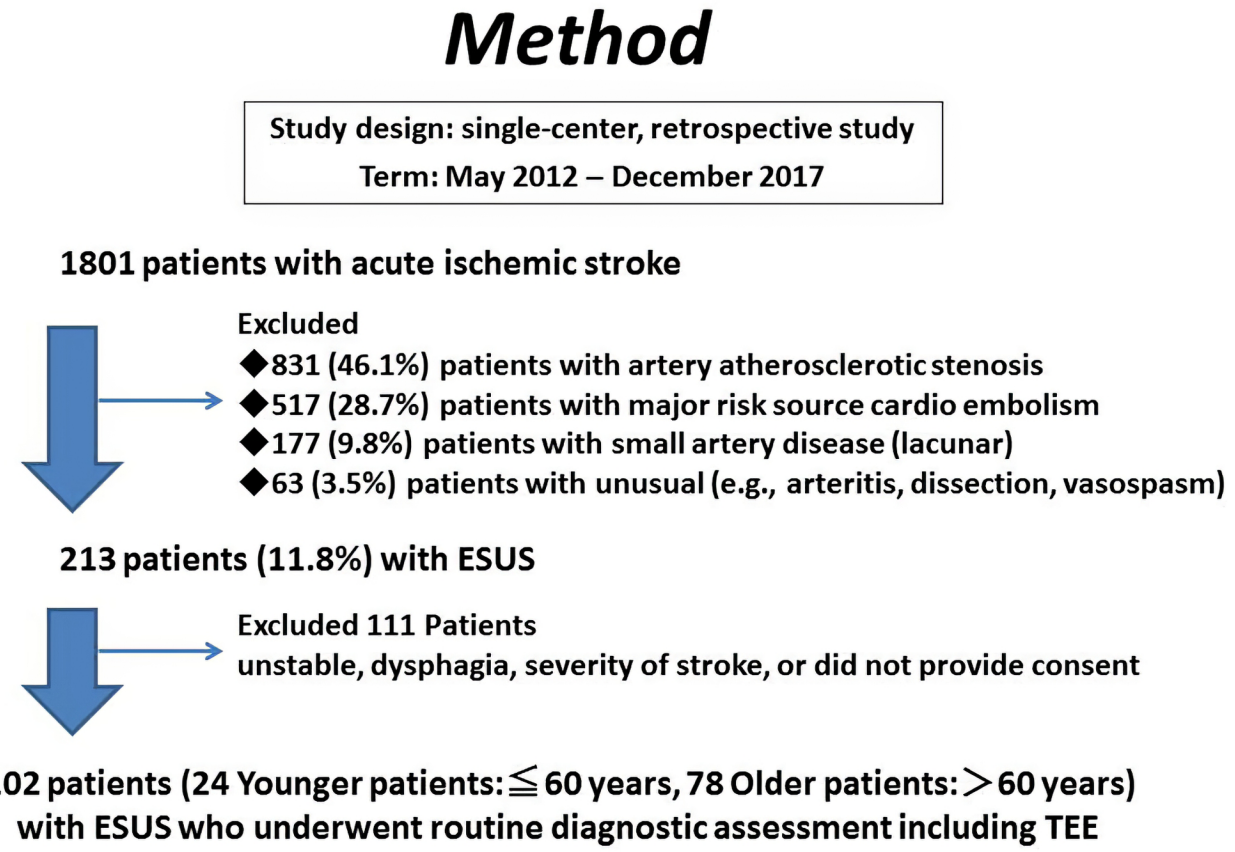

Figure 1. Study flowchart. ESUS: embolic stroke of undetermined sources; TEE: transesophageal echocardiography.

proposed diagnostic assessment for ESUS does not include routine use of transesophageal echocardiography (TEE).

Patent foramen ovale (PFO) is one of the causes of ESUS, especially in patients with paradoxical embolism. The relationship between paradoxical embolism and PFO is well documented. Conversely, the gold standard imaging tool in diagnosing PFO is TEE. In addition, percutaneous closure of PFO in patients with embolic strokes was recently deemed to be more effective than medical therapy alone [2, 3, 18]. In the current era of PFO closure, it is important to determine the specific embolic source. However, the distribution of embolic sources in patients with ESUS remains unclear. Additionally, the difference in embolic sources in patients with different ages is not well described. The aim of the present study was to investigate the distribution of embolic sources in patients with embolic strokes according to their age using routine diagnostic assessments including TEE and to evaluate the distribution of paradoxical embolism related to patent foramen ovale (PFO) between younger and older..

Materials and Methods

This was a single-center, retrospective study. Between May 2012 and December 2017, 1801 consecutive patients with acute ischemic stroke were admitted to the Tokushima Red Cross Hospital in Japan. Figure 1 shows the study flowchart. Of these 1801 patients, 213 (11.8%) fulfilled the ESUS diag-

Table 1. Patient characteristics according to age

	All patients (n=102)	Younger (n=24)	Older (n=78)	P value
Age, yrs	68.8±13.2	49.3±10.9	74.8±6.2	<0.001
Body mass index, kg/m^2	23.1±3.1	23.8±3.4	22.9±3.0	0.21
Male	71(69.6)	17(70.8)	54(69.2)	0.88
Hypertension	64(62.7)	7(29.2)	57(73.1)	<0.001
Diabetes mellitus	27(26.5)	7(29.2)	20(25.6)	0.73
Dyslipidemia	62(60.1)	15(62.5)	47(60.3)	0.84
Smoking history	53(51.9)	15(62.5)	38(48.7)	0.24
Previous stroke	18(17.6)	3(12.5)	15(19.2)	0.45
Af history	0(0)	0(0)	0(0)	-

Values are mean±SD, n (%).
Af: atrial fibrillation

nostic criteria and were classified according to the cause of embolic stroke [1]. Based on joint decision by a neurologist and cardiologist, 102 patients underwent routine diagnostic assessment with additional TEE to determine the specific cause of their embolic stroke. Patients who were unstable or did not provide consent were excluded. Moreover, we compared the cause of embolic stroke between younger (≤60 years; mean age, 49.3 ± 10.9 years; age range, 23–60 years; n=24) and older (>60 years; mean age, 74.8 ± 6.2 years; age range, 62–86 years; n=78) patients.

TEE examination and definitions of cardiac sources of embolism

TEE was performed to determine the specific embolic source, in addition to routine diagnostic assessment. An IE33 echocardiography system (Philips Medical Systems, Eindhoven, The Netherlands) with a multiplane transesophageal 5-MHz transducer was used. TEE was performed under sedation, and embolic sources were diagnosed by consensus of two experienced echocardiography specialists. PFO was defined as the presence of a right-to-left shunt using agitated saline contrast microbubbles within three cardiac cycles via a Valsalva maneuver with abdominal compression after complete opacification of the right atrium. TEE for detection of PFO was performed at the end of the examination after the anesthetic wore off. Atrial septal aneurysms (ASAs) were defined as an interatrial septum with a 10 mm protrusion into the right or left atrium and a diameter ≥15 mm at the base of the aneurysm. Reduced left atrial appendage blood flow (LAAF) was defined as <30 cm/sec. Aortic plaque was defined as plaque thickness >4 mm in the aortic arch or descending aorta. The total number of embolic sources was used to calculate the risk of stroke according to the ESUS criteria for embolic stroke [1].

Statistical analysis

Continuous variables are expressed as mean ± standard deviation. Categorical variables were compared between groups using the chi-squared or Fisher's exact tests. A p <0.05 was considered statistically significant. All data were analyzed using JMP version 8 (SAS Institute, Cary, NC).

Ethical approval

This present study has been approved by ethics standards of the institutional research, and the study was performed in accordance with the 1964 Declaration of Helsinki.

Results

Baseline characteristics

The baseline characteristics of the younger and older patients are shown in Table 1.The mean age of patients in this study was 68.8 ± 13.2 years and 71 (69.9%) were male. Compared with the younger patients, the rates of hypertension were significantly higher in the older patients. The prevalence of diabetes mellitus, dyslipidemia, smoking history, and previous stroke were similar between the younger and older patients. None of the patients in either group had a history of atrial fibrillation or flutter.

Distribution of embolic sources in patients with ESUS according to age

The various embolic sources are summarized in Table 2. The most frequent cause of embolic stroke was PFO (56.9%), followed by aortic arch atherosclerotic plaques (38.2%). No significant differences between the groups were found in the rates of minor-risk potential cardio embolic sources such as the

Table 2: Characteristics of the embolic sources.

Causes	All patients (n=102)	Younger (n=24)	Older (n=78)	P value
Minor-risk potential cardio embolic sources				
Mitral valve				
Myxomatous valvulopathy with prolapse (%)	1(0.9)	0(0)	1(1.3)	0.57
Mitral annular calcification (%)	3(2.9)	1(4.2)	2(2.6)	0.68
Aortic valve				
Aortic valve stenosis (%)	1(0.9)	0(0)	1(1.3)	0.57
Calcific aortic valve (%)	14(13.7)	1(4.2)	13(16.7)	0.12
Non-atrial fibrillation atrial dysrhythmias and stasis				
Atrial asystole and sick sinus syndrome (%)	2(1.9)	0(0)	2(2.6)	0.43
Atrial appendage stasis with reduced flow velocities or spontaneous echo densities (%)	5(4.9)	0(0)	5(6.4)	0.20
Atrial structural abnormalities				
Atrial septal aneurysm (%)	32(31.4)	4(16.7)	28(35.9)	0.07
Chiari network (%)	11(10.8)	1(4.2)	10(12.8)	0.23
Left ventricle				
Moderate systolic or diastolic dysfunction, Ventricular non-compaction, Endomyocardial fibrosis (%)	9(8.8)	2(8.3)	7(9.0)	0.92
Cancer-associated				
Convert non-bacterial thrombotic endocarditis , Tumor emboli from occult cancer (%)	4(3.9)	0(0)	4(5.1)	0.26
Arteriogenic emboli				
Aortic arch atherosclerotic plaques, Cerebral artery non-stenotic plaques with ulceration (%)	39(38.2)	1(4.2)	38(48.7)	<0.001
Paradoxical embolism				
Patent foramen ovale (%)	58(56.9)	15(62.5)	43(55.1)	0.52
Atrial septal defect (%)	3(2.9)	1(4.2)	2(2.6)	0.68
Pulmonary arteriovenous fistula (%)	0(0)	0(0)	0(0)	-

mitral valve, aortic valve, atrial structural abnormalities, and left ventricle. Similarly, no difference in cancer-associated and paradoxical emboli was observed between younger and older patients. PFO as the embolic source was also similar between younger and older patients (62.5% vs. 55.1%, p=0.52).On the other hand, the rate of aortic arch atherosclerotic plaques was significantly higher in older patients (4.2% vs. 48.7%, p <0.001).

Total numbers of other embolic sources in addition to PFO or combined PFO and ASA

A total of 58 patients (56.9%) were detected PFO. Table 3 presents the total number of other embolic sources in addition to PFO or combined PFO and ASA. Older patients exhibited multiple causes of embolic stroke more frequently than younger patients with only 14 of 43 (32.6%) having PFO or combined PFO and ASA alone.

Table 3. Total numbers of other embolic sources in addition to patent foramen ovale or combined patent foramen ovale and atrial septal aneurysm

	All patients (n=58)	Younger (n=15)	Older (n=43)	P value
Total numbers of other embolic sources in addition to PFO or combined PFO and ASA				0.017
0(%)	26(44.8)	12(80.0)	14(32.6)	-
1(%)	19(32.8)	2(13.3)	17(39.5)	-
2(%)	12(20.7)	1(6.7)	11(25.6)	-
3(%)	1(1.7)	0(0)	1(2.3)	-

PFO: patent foramen ovale; ASA: atrial septal aneurysm.

Discussion

TEE is superior to transthoracic echocardiography for identifying intracardiac abnormalities [4]. It is especially useful for identifying abnormal structures in detail, such as PFO and ASA, or other intracardiac embolic sources, such as LAAF, Chiari networks, and aortic valve calcification. A previous study has already shown the association between the presence of PFO and cryptogenic stroke in both older and younger patients [5]. However, it did not clearly evaluate other causes of ESUS except for PFO and ASA. Moreover, no other previous study has clearly assessed and classified the distribution of causes according to the ESUS criteria [1]. The present study utilized TEE to identify other causes of ESUS according to the ESUS criteria.

The prevalence of PFO on echocardiographic and autopsy studies in the healthy adult population is approximately 20%–25% [6-8]. Furthermore, approximately 40%–60% of cases of stroke with paradoxical embolism in young people are associated with PFO [8, 9, 19]. Notably, our study showed a higher incidence of PFO in ESUS patients compared with previous studies, which may be attributed to our definition of PFO, i.e., the presence of at least one microbubble in the left atrium within three cardiac cycles after opacification of the right atrium using agitated saline contrast microbubbles [9], regardless of the number of microbubbles. In addition, a previous study showed a positive relationship between the size of the shunt and the risk of stroke [10]. Some authors have indicated that PFO size can be defined by the number of microbubbles, where 3–10 microbubbles is a small shunt, 1–30 is a moderate shunt, and >30 is a large shunt [11]. Other previous studies have identified that the morphological or functional characteristics of PFO are associated with paradoxical embolic stroke [12, 13]. In our study, these elements of PFO were not evaluated; however, we evaluated the frequency of ASA and found that it was anatomically related to PFO. The coexistence of PFO and ASA is a stronger risk factor for stroke than either source by itself [14]. Our study demonstrated that the frequency of PFO or combined PFO and ASA without other cardioembolic sources was 80% and 32.6% in younger and older ESUS patients, respectively.

Three previous trials, the CLOSURE-1 trial (Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient ischemic Attack due to Presumed Paradoxical Embolism through a PFO) [15], the RESPECT trial (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) [16] and the PC trial (Randomized Clinical Trial Comparing the Efficacy of Percutaneous Closure of Patent Foramen Ovale With Medical Treatment in Patients With Cryptogenic Embolism) [17] did not show a superiority for PFO closure over medical therapy in patients with cryptogenic stroke. However, more recent trials showed that PFO closure is effective in preventing recurrent stroke [2, 3, 18]. These trials reported that the rates of recurrent stroke in younger (18–60 years) patients were significantly lower with closure of the PFO plus antiplatelet therapy than with antiplatelet therapy

alone. However, the clinical benefit of PFO closure for preventing recurrent stroke in older patients with stroke-related PFO has not been adequately evaluated. We believe that PFO closure in older patients might be considered if no causes of embolic source other than PFO and ASA are detected in patients with ESUS who undergo routine diagnostic assessment with additional TEE. Further study of larger numbers of ESUS patients is necessary to confirm our results.

Our study has several limitations. First, this was a single-center, retrospective study, which potentially introduces selection bias. Second, only a small number of patients were analyzed. Third, undetected causes, such as subclinical paroxysmal atrial fibrillation, may have existed in the study population. All patients of this study underwent cardiac monitoring for ≥24 h with automated rhythm detection and none had any atrial high rate episodes up until discharge. This is insufficient monitoring, especially in older patients because the current recommendation is 2-4 weeks of ECG monitoring. Forth, we did not have follow up on the older patients who had PFO closure. It is unknown whether PFO closure of older ESUS patients related PFO is efficacy same as younger. However, we believe that our study population reflects a real world unselected population of patients with ESUS.

Conclusion

The embolic sources of ESUS were similar between younger and older patients except for aortic arch atherosclerotic plaques. However, the total number of embolic sources was significantly higher in older patients. Therefore, it is difficult to determine a distinct single cause of stroke in older ESUS patients. Both younger patients and a small percentage of older patients have a risk of paradoxical embolism only, such as PFO or both PFO and ASA. Routine diagnostic assessment with additional TEE could help clarify the causes of ESUS.

Conflict of Interest

The authors have no conflict of interest relevant to this publication.

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