Prevalence of Patent Foramen Ovale in the Japanese Population

– Autopsy Study –

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Background: Patent foramen ovale (PFO) can cause ischemic stroke because of paradoxical embolism. Autopsy studies have shown that the prevalence of PFO is 25% in whites or blacks. However, there is a paucity of data on the prevalence of PFO in Asians. The aim of this study was to clarify the prevalence of PFO in the Japanese population.

Methods and Results: We reviewed 52,717 autopsy reports, which were collected and edited by the Japanese Society of Pathology from 2009 to 2012. Next, we inspected consecutive 103 formalin-fixed specimens that had already been examined by certified pathologists from 2009 to 2013 to find PFO and atrial septal aneurysm (ASA). ASA was defined as ≥ 10 mm protrusion of the septum into the left or the right atrium. In the database of the Japanese Society of Pathology, the incidence of PFO was 0.08% (43/52,717). Inspection of heart specimens disclosed that the prevalence of PFO was 13.6% (14/103). None of the PFO cases was reported at the original autopsy. PFO was more frequently found in the subjects with ASA (50%) than in those without ASA (9.7%) ($P=0.004$).

Conclusions: PFO is under-reported in autopsy reports. Re-evaluation of heart specimens disclosed that the prevalence of PFO was 13.6%. The prevalence was lower than reported in the past. (*Circ J* 2015; **79**: 2038–2042)

Key Words: Atrial septal aneurysm; Cryptogenic stroke; Ethnicity; Patent foramen ovale

Foramen ovale is an important cardiac structure for the fetal circulation between the right and left atria to provide oxygen-rich maternal blood to the fetal brain. In most cases it closes shortly after birth, but there are reports that it may still open in approximately 25% of adults.¹ The condition is called patent foramen ovale (PFO). Recently, PFO has been the focus of attention because it can be associated with increased risk of stroke.² Most PFO are benign and do no harm, but some PFO can open widely and enable thrombi to pass from the venous to arterial circulation. In addition to the embolic stroke, PFO has been linked to several other conditions, including migraine headache with aura, platypnea-orthodeoxia syndrome, decompression illness of divers, and sleep apnea.³

approximately 25% in whites or blacks.¹ However, there is a paucity of data on the Asian population. The aim of this study was to clarify the prevalence of PFO in the Japanese population from nationwide autopsy data and autopsy specimens of hearts.

Methods

First, we reviewed 52,717 autopsy cases to find PFO in the Annual Report edited by the Japanese Society of Pathology from 2009 to 2012. The Annual Report comprises nationwide data gathered from over 800 hospitals in Japan, where certified pathologists performed all the autopsies. The data include age, sex, primary disease related to the death, and autopsy findings.⁴

Then, we inspected consecutive 109 autopsy formalin-fixed and preserved heart specimens, which were already examined by certified pathologists from November 2009 to October

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Autopsy studies have shown that the prevalence of PFO is

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2013. Of the 109 hearts, 6 were excluded because the specimens were damaged by the search for the heart's conduction system. Finally, 103 hearts were re-examined for the presence of PFO and atrial septal aneurysm (ASA). The autopsy reports and clinical backgrounds of the subjects were reviewed using medical records. Two certified pathologists and a cardiologist (J.K., T.K., A.K.) inspected the heart specimens for the presence of PFO and ASA without interobserver variations. ASA was defined as ≥ 10 mm protrusion of the septum into the left or right atrium. The diameter and tunnel length of PFO were measured. The prevalence of PFO and ASA was compared among different age groups (≤ 59 , 60–79 and ≥ 80). The institutional review board of Keio University School of Medicine approved the protocol (approval no. 20140126).

Statistical Analysis

We present the quantitative data as mean value $\pm$ SD, and qualitative data as frequencies. We compared continuous variables using paired Student's t-test, and categorical variables by chi-square test or Fisher's exact test. All probability values are two-tailed and $P < 0.05$ was considered statistically significant. Statistical analysis was performed with Stat View (Stat View 5.0, Abacus Concepts Inc, Calabasus, CA, USA).

Results

In the Annual, the reported incidence of PFO was 0.08% (43/52,717). Of the 43 PFO cases, 30 patients were less than

Table 1. Characteristics of Japanese Autopsy Cases Examined for PFO and ASA

n	103
Age, years	69 (17–90)
Age ≥ 60 years	74 (72)
Male	72 (70)
Cause of death	
Malignancy	49 (48)
Liver failure	17 (17)
Cardiovascular	14 (14)
Infection	11 (11)
Collagen disease	3 (3)
Other	9 (9)

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

1 year old. The incidence of PFO cases older than 1 year old was 0.02% (13/52,717). In 1 case, paradoxical embolism because of PFO was reported.

Characteristics of the study population are shown in [Table 1](#). All were Asian. None of the cases of PFO or ASA was diagnosed before death. The prevalence of PFO and ASA was 13.6% (14/103) and 9.7% (10/103), respectively. PFO is more likely to coexist with ASA ([Figures 1,2](#)). None of the cases of PFO and ASA was discovered or reported at the original

Figure 1. Gross anatomy of patent foramen ovale (PFO) and atrial septal aneurysm (ASA). (A) View from the right atrium showing ASA. (B) View from the left atrium (same subject as in A). (C) View from the right atrium showing coexistence of ASA and PFO. A probe is inserted through the PFO. (D) View from the left atrium with the probe inserted.

autopsy. The prevalence of PFO did not differ among age groups ($P=0.2367$), whereas ASA was more frequently found in the subjects older than 80 years old ($P=0.0039$) (Table 2). The diameter of PFO ranged from 1 to 10 mm (mean 5.0 mm) and was larger on the left atrial side than on the right atrial side (5.9 mm vs. 4.3 mm, $P<0.005$). The mean tunnel length was 4.2 mm (2–11 mm). Most of the PFO had a flap-like shape, but the pinhole type was found in 1 case (Figure 3). There was no thrombus formation related to the PFO or ASA.

Discussion

The main findings of this study were that PFO and ASA are under-reported, and that the prevalence of PFO in both the nationwide database and the autopsy specimens was lower than reported in the past.

PFO has been generally regarded as a benign condition and seen in approximately 25% of the general population. Recently, however, the association of PFO with several diseases has been recognized, including paradoxical embolism, migraine headache with aura, platypnea-orthodeoxia syndrome, decom-

Table 2. Prevalence of PFO and ASA According to Age in Japanese Autopsy Series				
	≤59	60–79	≥80	P value
n	29	58	16	
PFO, n (%)	2 (7.0)	8 (13.8)	4 (25.0)	0.2
ASA, n (%)	3 (10.3)	2 (3.4)	5 (31.3)	0.004

Abbreviations as in Table 1.

Table 3. Prevalence of PFO in Autopsy Studies

Year	Authors	No. of hearts	Prevalence of PFO (%)	Origin
1897	Parsons and Keith ¹³	399	26	London, UK
1900	Fawcett and Blachford ¹⁴	306	32	Bristol, UK
1930	Thompson and Evans ¹⁵	977	27	London, UK
1934	Seib ¹⁶	500	17	Minnesota, USA
1948	Wright et al ¹⁷	492	23	Illinois, USA
1972	Schroeckenstein et al ¹⁸	144	35	Minnesota, USA
1979	Sweeney and Rosenquist ¹⁹	64	31	Nebraska, USA
1984	Hagen et al ¹	965	27	Minnesota, USA
1994	Penther ²⁰	500	15	Brest, France
Total		4,347	25	

Abbreviation as in Table 1.

Table 4. Prevalence of PFO in Adult Autopsy Studies

Year	Authors	No. of hearts	Prevalence of PFO (%)	Origin
1897	Parsons and Keith ¹³	139	28	London, UK
1900	Fawcett and Blachford ¹⁴	300	31	Bristol, UK
1934	Seib ¹⁶	500	17	Minnesota, USA
1979	Sweeney and Rosenquist ¹⁹	64	31	Nebraska, USA
1994	Penther ²⁰	500	15	Brest, France
Total		1,503	21	

Abbreviation as in Table 1.

pression illness of divers, and sleep apnea.² Of these conditions, the most devastating complications are paradoxical embolism leading to stroke, myocardial infarction, or infarct of other vital organs. Thus, for prevention of paradoxical embolism, transcatheter PFO closure has been performed worldwide.^{5–10} Our study indicates that paradoxical embolism is a rare event for most Japanese subjects with PFO. In the autopsy cases, there were no paradoxical emboli and only 1 case in the nationwide database was identified as paradoxical embolism because of PFO. However, PFO is clearly under-reported, which means that clinicians and pathologists have a low awareness of paradoxical embolism caused by this structure.

For patients with stroke of unknown etiology, a transesophageal cardiac ultrasound study showed that the frequency of PFO was similar among whites (34%), blacks (31%), and Hispanics (37%).¹¹ However, their subjects did not include Asians. Another study using transthoracic cardiac ultrasound disclosed a lower prevalence of PFO in Indo-Asians (2%) compared with whites (2.4%) or blacks (7%), but the overall prevalence of PFO was lower than expected in their study (2%), possibly because of the lower diagnostic sensitivity of transthoracic cardiac ultrasound.¹² Autopsy is a most precise method for detecting PFO and its prevalence in past autopsy studies was 24.6% overall (Table 3).^{1,13–20} Most of those reports included specimens from infants. If they are limited to adults,^{13,14,16,19,20} the prevalence is lower (20.6%), possibly because some PFO close after 1 year of age (Table 4). In the Japanese nationwide database, PFO was reported in only 0.08%. In the hospital autopsy cases, PFO was not identified in the original reports. Unless special attention is paid, PFO can be easily overlooked. Re-inspection revealed that the prevalence of PFO was 13.6%, the lowest among the autopsy reports (Figure 4).

In our study, PFO was strongly associated with ASA: PFO

was found in 50% of patients with ASA, but in 9.7% of patients without ASA, which is in line with the literature. The odds of PFO are 4.6-fold greater with ASA than without ASA.²¹ A small PFO may be missed by transthoracic cardiac ultrasound, but ASA is easier to find. If we encounter ASA in patients with cryptogenic stroke, PFO should be thoroughly searched for. Because PFO is an important cause of paradoxical embolic stroke, especially in the young population, special attention should be paid at cardiac ultrasound as well as autopsy.

Study Limitations

An important limitation of this study is that it was an autopsy

study. It may not represent the general population. Second, the number of re-inspected cases was small and the age of the population was relatively high compared with previous studies. Depending on the age of population, the prevalence could be different. Finally, we did not make a direct comparison of the prevalence of PFO among different ethnic groups because our study included only an Asian population.

Conclusions

At autopsy, PFO was under-reported. In a re-evaluation of the Japanese autopsy hearts, we found PFO in 13.6%, which was lower than reported in the past.

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