Identification of High-Risk Patent Foramen Ovale Associated with Cryptogenic Stroke: Development a Scoring System

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Abstract

Background: Transcatheter closure of patent foramen ovale (PFO) has become an effective therapeutic strategy for cryptogenic stroke (CS). The identification of high-risk PFO is essential, but the data are limited. This study aimed to clarify the factors related to CS, and to develop the score of high-risk PFO.

Methods: We retrospectively analyzed 57 patients with prior CS and 50 without CS who were scheduled for transcatheter closure. PFO characteristics were evaluated by transesophageal echocardiography. Based on factors related to CS, we estimated the risk score.

Results: Patients with CS had a greater frequency of the large size PFO (≥2 mm of height), the long tunnel PFO (≥10 mm of length), atrial septal aneurysm, hypermobile interatrial septum, prominent Eustachian valve or Chiari's network, the large right-to-left shunt at rest and during Valsalva maneuver, and the low angle PFO (≤10° of PFO angle from inferior vena cava), compared with patients without CS. Multivariate analysis showed that the long tunnel PFO, the presence of hypermobile interatrial septum, the presence of prominent Eustachian valve or Chiari's network, the large right-to-left shunt during Valsalva maneuver, and the low angle PFO were independently related to CS. When the score was estimated based on 1 point for each factor, the proportion of CS was markedly elevated with the score of ≥2 points. The probability of CS was markedly different between scores of ≤1 or ≥2 points.

Conclusions: PFO risk can be assessed with a score based on high-risk features. The presence of 2 or more high-risk PFO features is associated with CS.

Key Words: cryptogenic stroke, echocardiography, patent foramen ovale, transcatheter closure

Abbreviations and Acronyms

ASA = atrial septal aneurysm

CS = cryptogenic stroke

IVC = inferior vena cava

PFO = patent foramen ovale

RL = right-to-left

TEE = transesophageal echocardiography

Introduction

Patent foramen ovale (PFO) is linked with various diseases, including cryptogenic stroke (CS) and migraine (1-6). The relationship between PFO and CS has become particular interest, based on recent trials demonstrating that transcatheter PFO closure can reduce the recurrence of stroke compared with medical therapy (7-9). The prevalence of PFO is approximately 25% of the general population (10), but not all PFOs involve CS. As transcatheter closure would be expanded as the therapeutic option, it is important to identify cases of the high-risk PFO who are most likely to associate with CS. However, there are limited data on the comprehensive assessment of PFO morphology associated with the development of CS (11,12). This study aimed to compare the anatomical and functional characteristics of PFO using transesophageal echocardiography (TEE) between patients with CS and those without CS, and to clarify the factors related to CS. Furthermore, this study aimed to develop the scoring system for the identification of high-risk PFO.

Methods

Study population.

We retrospectively enrolled 107 consecutive patients with PFO who were scheduled transcatheter closure for CS or migraine from May 2008 to December 2017. Patients with CS were proven cerebral infarction using magnetic resonance imaging (MRI). CS was diagnosed by a neurologist based on the exclusion of all other identifiable causes of stroke such as large artery atherosclerosis, cardioembolism, small vessel disease, or arterial dissection after clinical examinations including brain and carotid imaging, electrocardiography, and echocardiography. Patients with CS who were suspected PFO were referred to our institution to assess for indication of transcatheter closure. All patients underwent TEE to identify the presence of PFO. When PFO was detected and the other causes of CS were excluded, transcatheter closure was scheduled. Migraine was diagnosed according to the criteria of the International Headache Society (13). Patients with migraine underwent MRI and were confirmed to have no cerebral infarct lesion. They were referred to our institution to assess for indication of transcatheter PFO closure. Patients who were detected PFO by TEE were scheduled for transcatheter closure. This study classified patients with migraine as the group of PFO patients without CS. All patients gave written informed consent for the examinations. The study was approved by the ethical committee of our institution.

Echocardiography.

TEE was performed for PFO diagnosis before transcatheter closure using iE33 with an X7-2t probe (Philips Medical Systems, Andover, Massachusetts, USA) under local anesthesia. Intravenous sedation was administrated if needed, although patients remained able to follow instructions for Valsalva maneuver. The presence of PFO was confirmed when microbubbles crossed from the right to left atrium within 3 cardiac cycles after opacification of the right atrium, using intravenous injection of agitated saline contrast. The anatomical and functional characteristics of PFO, such as the height of PFO, the length of PFO tunnel, the presence of atrial septal aneurysm (ASA), the presence of hypermobile interatrial septum, the presence of prominent Eustachian valve or Chiari's network, the grade of right-to-left (RL) shunt at rest and during Valsalva maneuver, and the angle between inferior vena cava (IVC) and PFO, were evaluated by independent cardiologists who were unaware of the CS status of the patient. The height of PFO was measured by the maximum separation between the septum primum and septum secundum in the end-systolic frame (Figure 1A), and ≥2 mm of the height was defined as the large size PFO (14). The length of PFO tunnel was measured by the maximum overlap between the septum primum and septum secundum (Figure 1B), and ≥10 mm of the length was defined as the long tunnel PFO (11). ASA was defined as ≥10 mm of septal excursion from the midline into the right or left atrium, or ≥15 mm of total excursion between the right and left atrium (1). We also defined the moving and floppy septum with ≥5 mm of septal excursion in every heartbeat as hypermobile interatrial septum (Figure 1C). The presence of prominent Eustachian valve was defined as ≥10 mm protrusion within the right atrium (15). The grade of RL shunt was assessed at rest and during Valsalva maneuver using agitated saline contrast. The maximum number of microbubbles that appeared in the left atrium was counted in a single frame (Figure 1D), and the large RL shunt was defined as ≥20 microbubbles (1,8). We measured the angle between IVC and PFO flap on an imaging plane that displayed the IVC and interatrial septum (Figure 1E), and ≤10° of the PFO angle from IVC was defined as the low angle PFO.

Statistical analysis.

Data are presented as mean ± standard deviation for continuous variables and as number and percentage for categorical variables. Differences between the 2 groups were analyzed by the *t* test and Mann-Whitney *U* test for continuous variables and the χ^2 test for categorical variables. Univariate and multivariate logistic analysis was performed to identify independent factors related to CS. Variables for analysis included the large size PFO, the long tunnel PFO, the presence of hypermobile interatrial septum, the presence of prominent Eustachian valve or Chiari's network, the large RL shunt during Valsalva maneuver, and the low angle PFO. Odds ratios are shown with 95% confidence intervals. Based on the results of multivariate analysis, the score of high-risk PFO was estimated. Statistical analysis was performed with statistical software (JMP version 11.0; SAS Institute Inc., Cary, NC, USA), and significance was defined as a value of $p < 0.05$.

Inter- and intra-observer differences were analyzed in 20 randomly selected images. The length of PFO tunnel, the presence of hypermobile interatrial septum, and the large RL shunt during Valsalva maneuver were evaluated by 2 blinded observers and by a single observer at 2 different times. Reliability was calculated by Pearson's correlation coefficient. Variability was calculated as the percentage error of each measurement and derived as the difference between the 2 measurements divided by the mean value.

Results

Patient characteristics.

The mean age of all patients was 45 ± 15 years. Comparisons of patient characteristics between 57 patients with CS and 50 without CS are shown in Table 1. Patients with CS were older than those without CS. The prevalence of hypertension was higher in patients with CS than in those without CS.

Echocardiographic characteristics of PFO.

Comparisons of the anatomical and functional characteristics of PFO between the 2 groups are shown in Table 2. The height of PFO was greater in patients with CS than in those without CS, and the large size PFO (≥2 mm) was more frequently observed in patients with CS. While the long tunnel PFO (≥10 mm) was more frequently observed in patients with CS than in those without CS, there was no difference in the mean length of PFO tunnel between the 2 groups. This was because short tunnel PFO (≤ 2 mm) was also frequent in patients with CS.

Patients with CS more frequently had ASA, hypermobile interatrial septum, and prominent Eustachian valve or Chiari's network compared with those without CS. The large RL shunt at rest and during Valsalva maneuver was more frequently observed in patients with CS than in those without CS. The angle between IVC and PFO was lower in patients with CS than in those without CS, and the low angle PFO (≤10°) was more frequently observed in patients with CS.

Factors related to CS.

Multivariate logistic analysis showed that the long tunnel PFO, the presence of hypermobile interatrial septum, the presence of prominent Eustachian valve or Chiari's network, the large RL shunt during Valsalva maneuver, and the low angle PFO were independently related to CS (Table 3). When age and the prevalence of hypertension were added as variables to multivariate logistic analysis, the same echocardiographic factors were independently related to CS. Age or the prevalence of hypertension were not related (Table 3).

High-risk PFO score

By scoring each independent factor related to CS as 1 point (Table 4), we estimated the score of high-risk PFO. The proportion of patients with CS and those without CS according to the score is shown in Figure 2. The proportion of CS was 5% or 17% at the score of 0 or 1 point respectively. However, the proportion of CS was markedly elevated at the score of ≥2 points, with 80%, 87%, or 89% at the score of 2, 3, or 4 points, respectively. The probability of CS was also markedly different between scores of ≤1 or≥2 points. The score of 2 points had 91% sensitivity and 80% specificity for the association with CS. The false positive rate and the false negative rate were 20% and 9%, respectively. Among patients with CS who had the score of ≥2 points, the individual components related to CS are shown in Figure 3. The presence of hypermobile interatrial septum and the large RL shunt during Valsalva maneuver were strongly related to CS.

Reproducibility

There was good agreement in the measurements of the length of PFO tunnel between the 2 blinded observers ($r = 0.98$, $p < 0.001$), and for the intra-observer ($r = 0.97$, $p < 0.001$). The inter- and intra-observer variabilities for the length of PFO tunnel were 4.8% and 5.1%, respectively. There was 100% agreement in the classification of the hypermobile interatrial septum and also the large RL shunt during Valsalva maneuver by both the 2 blinded observers, and single observer assessing twice.

Discussion

The present study evaluated the anatomical and functional characteristics of PFO in patients with CS and those without CS. The major findings were as follows: 1) the long tunnel PFO, the presence of hypermobile interatrial septum, the presence of prominent Eustachian valve or Chiari's network, the large RL shunt during Valsalva maneuver, and the low angle PFO were the independent factors related to CS; and 2) PFO with a score ≥2 points was associated with CS when the score was estimated based on 1 point for each factor. To the best of our knowledge, this is the first study to develop the score of high-risk PFO associated with CS.

Factors related to CS.

Because transcatheter PFO closure has recently become an effective therapy for stroke, accurate diagnosis of PFO is needed (16,17). Furthermore, it is essential to stratify PFO for an increased risk of CS. Previous studies have reported that the large size PFO, the large RL shunt, and the presence of ASA were risk factors for an increased likelihood that PFO was causally linked to CS (11,18-20). The presence of prominent Eustachian valve or Chiari's network was also reported to be more common in patients with CS (21,22). Nevertheless, there were conflicting reports showing no relationships (23), and the characteristics of PFO related to CS remain controversial. In addition, the detailed assessment of PFO morphology using echocardiography has not been fully investigated.

In the present study, the large RL shunt during Valsalva maneuver was related to CS, whereas the large size PFO was not related. This observation may relate to the fact that PFO size was measured at rest. The opening of PFO can enlarge when the pressure in the right atrium exceeds that in the left atrium due to Valsalva maneuver, thereby increasing the potential for thrombus passage from the venous to arterial circulation. Thus, assessment of the maximum PFO size induced by Valsalva maneuver may be useful to assess the probability of CS.

This study found that the presence of hypermobile interatrial septum was related to CS. Hypermobile interatrial septum, which is the floppy septum with movement of free edge in every heartbeat, can often cause enlargement of PFO orifice, leading to an increase in the potential for thrombus passage. Indeed, ASA was observed in 40% of patients with CS, while hypermobile interatrial septum was observed in 70%. Our findings suggest that the presence of hypermobile interatrial septum should be carefully evaluated using TEE.

The presence of prominent Eustachian valve or Chiari’s network was also related to CS in this study. Eustachian valve is an embryological remnant of the valve that prenatally directs blood flow from IVC to fossa ovalis of septum. Chiari’s network is a mobile structure that extends from the junction of IVC and right atrium to septum. Both structures can direct IVC blood flow through PFO and predispose to CS. The mechanism of CS may also relate to the angle between the IVC and PFO. Indeed, we provide new evidence that the low angle between the IVC and PFO was related to CS. The low angle may preferentially direct IVC blood flow towards the interatrial septum and PFO orifice.

Similar to the previous study (11), this study showed that the long tunnel PFO was related to CS. The septal pouch on the left side of interatrial septum was reported to be associated with CS caused by thrombus formation (24). The long tunnel PFO might also be the site for thrombus formation because of turbulent and stagnant blood flow (11). In contrast, patients with CS have also been reported to have the short tunnel PFO (25). Thus, further studies are required to elucidate the relationship between the length of PFO tunnel and CS, and to identify the mechanisms.

Clinical implications.

Recent randomized trials demonstrated the benefits of transcatheter closure for the reduction of stroke compared with medical therapy (7-9), although the earlier trials such as CLOSURE I, PC, and RESPECT failed to show the superiority (26-28). These discrepancies between the earlier negative trials and recent positive trials are thought to relate to patient selection for transcatheter PFO closure. Because PFO is a frequent finding (10), the identification of high-risk PFO is important. There are likely multiple factors involved in the role of PFO in causing CS. Thus, the scoring system using these factors may be useful for clinical stratification of PFO. In the present study, we developed the scoring system for the identification of high risk PFO associated with CS, with each factor related to CS scored as 1 point. The association with CS was low at the score of 0 or 1 point, but it was markedly elevated at the score of ≥2 points. Indeed, at the score of 2 points, the sensitivity and the specificity for the association of PFO with CS was 91% and 80%, respectively. These findings suggest that the score of ≥2 points is clinically useful for stratifying PFO for risk of developing of CS, and thus for selection of appropriate patients for PFO closure.

Study limitations.

There are several limitations in the present study. First, this was a retrospective cohort study. Thus, the score was not assessed to predict who will develop a CS. Second, there was selection bias because only patients who were scheduled for transcatheter PFO closure were selected. Therefore, our study population had a high proportion of high-risk subjects, and was not representative of the general population with PFO. A larger study, including patients who were not considered for transcatheter closure, is required to confirm our findings. Third, neurologically asymptomatic subjects who had a PFO on TEE would be the ideal control or comparison group but for this study we used patients with migraine as the control group. Fourth, the grade of RL shunt might be underestimated because it depends on the degree of Valsalva maneuver. However, the TEE and Valsalva assessment were performed uniformly by the operators at our institution. Lastly, the number of cases may be too small to determine in the multivariate analysis whether certain components in the score should have different weights.

Conclusions

The long tunnel PFO, the presence of hypermobile interatrial septum, the presence of prominent Eustachian valve or Chiari's network, the large RL shunt during Valsalva maneuver, and the low angle PFO were related to CS. When 2 or more of these features are present on TEE, there is a strong association with CS. Thus, a score that accounts for the presence of these PFO features may be valuable for identifying patients with PFO at high-risk CS.

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Figure legends

Figure 1. PFO characteristics

(A) The height of PFO was measured by the maximum separation (arrow). (B) The length of PFO tunnel was measured by the maximum overlap (arrow). (C) The moving and floppy septum was defined as hypermobile interatrial septum. (D) The maximum number of microbubbles was counted. (E) The angle between IVC and PFO was measured.

IVC = inferior vena cava, LA = left atrium, PFO = patent foramen ovale, RA = right atrium.

Figure 2. High-risk PFO score

The proportion of patients with CS and those without CS was assessed based on the scoring system. The proportion of CS was low at the score of 0 or 1 point, but it was markedly elevated at the score of ≥2 points.

CS = cryptogenic stroke, PFO = patent foramen ovale.

Figure 3. Individual components related to CS

The individual components related to CS in patients with CS who had the score of ≥2 points were shown.

CS = cryptogenic stroke.