RoPE Score as a Predictor of Recurrent Ischemic Events After Percutaneous Patent Foramen Ovale Closure

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Summary

The benefits of patent foramen ovale (PFO) closure for cryptogenic stroke secondary prevention are still debated. The Risk of Paradoxical Embolism (RoPE) study developed a score to improve patient selection for this procedure. We proposed to assess the validity of this score to assess the prognostic impact of PFO closure.

From 2000 to 2014, all consecutive patients submitted to PFO closure were included in a prospective registry in a university center. The primary endpoint was recurrent ischemic cerebrovascular events and the secondary endpoints were all-cause, neurological, and cardiac mortality rates and new-onset atrial fibrillation (NOAF) rates. In total, 403 patients were included in the study (women: 52.1%; mean age: 44.7 ± 10.9 years). The mean follow-up period was 6.4 ± 3.7 years. Immediate success was achieved in 97% patients. There were 23 (5.8%) ischemic cerebrovascular events, 8 (2.0%) deaths, and 17 (4.3%) NOAFs. The mean RoPE score was 6.10 ± 1.79. Smoker status, coronary artery disease, lower RoPE score, and higher left atrial dimensions were predictors of the primary endpoint. However, a lower RoPE score and coronary artery disease remained independent predictors in multivariate analysis.

RoPE score was shown to be an independent predictor of recurrent ischemic cerebrovascular events, and a score of ≤ 6 was shown to identify patients with significantly higher risk of mortality and recurrent ischemic events.

Key words: Secondary prevention, Cryptogenic stroke

Stroke is the most common cause of mortality and morbidity in developed countries.10 Despite recent advancement in multimodality imaging, stroke etiology remains unknown (cryptogenic stroke) in a significant proportion of patients, ranging from 30% to 40% of cases.2,3 Research has shown an association between patent foramen ovale (PFO) and cryptogenic stroke in younger2-4 and older patients.5,6 Studies support the concept of paradoxical embolism through the PFO as a cause of cryptogenic stroke.7 Therefore, PFO closure has been postulated as a definitive therapeutic option for secondary prevention, reducing further embolic events in this patient population.5,9

Although observational studies have established an advantage of PFO closure over medical therapy, 3 randomized trials (CLOSURE, PC TRIAL, and RESPECT) failed to prove a statistically significant benefit of this technique for the secondary prevention of cryptogenic stroke in the intention-to-treat analysis.3-12 However, the RESPECT trial proved a significant benefit of percutaneous PFO closure over medical treatment in the per-protocol and as-treated analyses.9 Meta-analyses derived from both observational and randomized trials have reported ambiguous results.13-16 The low rate of recurrent ischemic events in these studies has been pointed as an explanation for the non-superior effect of PFO closure.17 Moreover, in result of the common prevalence of PFO in the general population (around 25%), it is difficult to infer if the presence of a PFO is related to the index ischemic event or an incidental finding.18 Recently, the results of an extended follow-up of the RESPECT trial cohort were presented, which showed a significant reduction in the PFO-related recurrent stroke rate in the device group compared with the medical treatment group.19

Kent, et al. suggested that the probability of a PFO being accountable for a cryptogenic stroke could be predicted based on a combination of classical cardiovascular risk factors and age.20 Therefore, the Risk of Paradoxical Embolism (RoPE) study combined data from 12 existing databases to extract a score that can identify a PFO-related stroke.17,21

This study aimed to determine the prognostic impact...
of PFO closure in a real-world population and to assess the RoPE score application to predict the recurrence rate of ischemic cerebrovascular events.

Methods

Population and definitions: From 2000 to 2014, all consecutive adult patients submitted to percutaneous PFO closure in the Grown-up Congenital Heart Disease departments of a single university center were enrolled in a prospective registry. All patients were referred for this procedure following the diagnosis of one or more acute ischemic cerebrovascular events. Ischemic events were classified as stroke when clinical neurological deficit lasted more than 24 hours and cerebral infarction was present in a magnetic resonance imaging (MRI) or computed tomography (CT) and as transient ischemic attack (TIA) when a neurological deficit lasting less than 24 hours was confirmed by a neurologist or specialized physician.

Clinical and demographic characteristics were obtained before the procedure. Patients with cerebrovascular ischemic events underwent a comprehensive etiological investigation by CT, MRI, transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE), carotid and transcranial Doppler imaging, and 24-hour heart rhythm monitoring. Moreover, prothrombotic states were searched when justified and ongoing medications, such as antithrombotic agents, were registered.

The present study was conducted in accordance to the principles of the Declaration of Helsinki. Informed consent was obtained from all the study patients. The study was approved by the local Medical Ethics Committee.

Procedure: PFO diagnosis, size, and anatomical features were studied by TEE before the procedure and the closure device type and size were chosen in accordance. Devices used included Amplatzer septal occluder®, Premere® (St Jude Medical, Plymouth, MN, USA), and Ultrasound Atrial Septal Defect Occluder® (Cardia, Eagen, MN, USA).

Patients submitted to percutaneous PFO closure were discharged on the following day in uneventful cases. Local or general anesthesia was used considering the patient and PFO characteristics. Device implantation was guided by fluoroscopy, TTE, and/or TEE, as needed. The procedure was performed under full heparinization and endocarditis prophylaxis.

Antithrombotic regimen with 6 months to life-long acetylsalicylic acid 100 mg, and 1 to 3 months clopidogrel 75 mg, was prescribed according to the bleeding risk profile of the patient. Endocarditis prophylaxis was recommended for all patients with an implanted device in the first 6 months after the procedure.

RoPE calculation: The RoPE score was calculated for all patients, as established in literature. A one-point system was given for each of the following: no arterial hypertension, diabetes mellitus, history of stroke or TIA, and non-smoking status, and presenting a cortically located cerebral infarction established by the neuro-radiology imaging workup. Zero to 5 points were added according to the patient’s age at the index ischemic event moment (0 for > 70; 1 for 60-69; 2 for 50-59; 3 for 40-49; 4 for 30-39; and 5 for 18-29 years). The threshold of 6, corresponding to our population RoPE score median and according to other studies, was used to categorize the patients into 2 groups: those with a high (> 6) and those with a low RoPE score (≤ 6).

Outcomes and clinical endpoints: Procedure success was evaluated immediately after the procedure by fluoroscopy and echocardiography (TTE or TEE). Success was defined by adequate device implantation, no interference with adjacent heart structures, and with none or minimal immediate residual shunt. All patients had a pre-discharge TTE examination to assess device position and residual shunt, as well as to rule out complications. Those patients followed up in our Cardiology Center also had an onsite first- and sixth-month TEE control and a first-year transesophageal echocardiographic examination to assess for the presence of residual shunt. Patients followed up outside our Cardiology Center and referred only for the procedure performed this imaging follow-up at the origin site and were sent back for reevaluation if a device complication or residual shunt was detected.

The primary clinical endpoint was defined as the recurrence of ischemic cerebrovascular events (stroke or TIA). Secondary endpoints included all-cause, neurological, and cardiac mortality rates and new-onset atrial fibrillation (NOAF) rates. These endpoints were compared between the groups with high and low RoPE scores.

Statistical analysis: Baseline demographic and clinical data are described as mean ± standard deviation for continuous variables and as frequency and percentage for categorical variables.

Normality (Gaussian distribution) was tested in all continuous variables using the Shapiro-Wilk test. RoPE score and age showed a normal distribution (post-hoc). To assess the association between RoPE score and continuous variables, we used Pearson correlation for non-normally distributed variables and Spearman correlation for normally distributed variables. To compare the RoPE scores between the groups, we used Student t-test for normally distributed variables and Mann-Whitney test for non-normally distributed variables. To evaluate the potential independent association between RoPE scores and clinical endpoints and construct predictive models, we used univariate and multivariate Cox regression. We set our significance level α at 0.05. Data were analyzed using the Statistical Package for the Social Science for Windows, version 20.0 (SPSS Inc., Chicago, IL).

Results

Population: From 2000 to 2014, 403 patients underwent an attempt of percutaneous PFO closure in our Interventional Cardiology Department. The mean age of the study population was 44.7 ± 10.9 years, and 52.1% of them were women. The index ischemic event was a stroke in 68.9% and a TIA in 31.1% of patients. PFO diagnosis was made by TEE in all patients, and 49.1% of patients presented with an interatrial septal aneurysm. Table I details the clinical, demographic, and procedural characteristics of the full cohort and the high and low RoPE score groups.
**Table I.** Baseline Clinic, Echocardiographic, and Procedure Characteristics of Total Cohort and Low and High RoPE Score Groups

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Total cohort ( (n = 403) )</th>
<th>RoPE &gt; 6 ( (n = 174) )</th>
<th>RoPE ≤ 6 ( (n = 229) )</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>44.72 ± 10.99</td>
<td>36.40 ± 7.52</td>
<td>51.15 ± 8.72</td>
<td>0.001</td>
</tr>
<tr>
<td>Female (( n/% ))</td>
<td>210 (52.1)</td>
<td>105 (60.5)</td>
<td>105 (54.1)</td>
<td>0.005</td>
</tr>
<tr>
<td>Diabetes (( n/% ))</td>
<td>19 (4.7)</td>
<td>0 (0.0)</td>
<td>19 (8.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension (( n/% ))</td>
<td>95 (23.6)</td>
<td>5 (2.9)</td>
<td>90 (39.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Dyslipidemia (( n/% ))</td>
<td>168 (41.7)</td>
<td>51 (29.3)</td>
<td>117 (51.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoker (( n/% ))</td>
<td>77 (19.1)</td>
<td>28 (16.1)</td>
<td>49 (21.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>Previous stroke/TIA (( n/% ))</td>
<td>55 (13.6)</td>
<td>12 (6.9)</td>
<td>43 (18.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>CAD (( n/% ))</td>
<td>10 (2.5)</td>
<td>2 (1.1)</td>
<td>8 (3.5)</td>
<td>0.11</td>
</tr>
<tr>
<td>Oral contraceptives (( n/% ))</td>
<td>46 (11.4)</td>
<td>33 (19.0)</td>
<td>13 (5.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Migraine (( n/% ))</td>
<td>54 (13.4)</td>
<td>33 (19.0)</td>
<td>21 (9.2)</td>
<td>0.026</td>
</tr>
<tr>
<td>Stroke (( n/% ))</td>
<td>278 (68.9)</td>
<td>121 (69.5)</td>
<td>156 (68.1)</td>
<td>0.99</td>
</tr>
<tr>
<td>TIA (( n/% ))</td>
<td>125 (31.1)</td>
<td>53 (30.5)</td>
<td>73 (31.8)</td>
<td>0.99</td>
</tr>
<tr>
<td>RoPE (mean ± SD)</td>
<td>6.10 ± 1.79</td>
<td>7.78 ± 0.80</td>
<td>4.82 ± 1.16</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Echocardiographic and procedure characteristics**

| TEE guided (\( n/\% \)) | 149 (36.9) | 67 (38.5) | 82 (35.8) | 0.60  |
| General anesthesia (\( n/\% \)) | 149 (36.9) | 67 (38.5) | 82 (35.8) | 0.60  |
| IASA (\( n/\% \))       | 198 (49.1) | 88 (50.6) | 110 (48.0) | 0.61  |
| LA diameter (mm) (mean ± SD) | 35.98 ± 5.18 | 34.61 ± 5.10 | 37.17 ± 4.97 | 0.001  |
| PFO diameter (mm) (mean ± SD) | 8.96 ± 2.91 | 9.23 ± 2.76 | 8.76 ± 3.01 | 0.13  |
| Amplatzer (\( n/\% \))   | 332 (82.3) | 139 (79.9) | 193 (84.2) | 0.22  |
| Ultraspt (\( n/\% \))    | 48 (12.0)  | 22 (12.6)  | 26 (11.4)  | 0.75  |
| Premere (\( n/\% \))     | 23 (5.7)   | 13 (7.5)   | 10 (4.4)   | 0.26  |
| Procedure success (\( n/\% \)) | 12 (97.0) | 168 (96.6) | 223 (97.4) | 0.99  |

SD indicates standard deviation; RoPE, Risk of Paradoxical Embolism Score; TIA, transient ischemic attack; CAD, coronary artery disease; TEE, tranesophageal echocardiography; IASA, interatrial septal aneurysm; LA, left atria; and PFO, patent foramen ovale.

**Procedure:** Percutaneous closure of PFO was performed under fluoroscopic guidance in all patients. TEE was performed in 36.9% of the patients under general anesthesia in the remainder under local anesthesia. The Amplatzer® was the most common device used for percutaneous closure of PFO (82.3%), followed by the Ultraspt® in 12.0% and the Premere® in 5.7% of patients. Procedure success with good device placement, no interference with other cardiac structures, and no or mild shunt was achieved in 97.0% of cases. Only 2 patients (0.49%) presented with major vascular access complications requiring surgical treatment.

**Outcomes and clinical endpoints:** The mean follow-up period was 6.4 ± 3.7 years (minimum: 1.1, maximum: 14.0 years), and 8 (1.9%) patients were lost to follow-up. First-year TEE was performed in 252 (62.5%) patients, of whom 18 (7.1%) presented with a residual shunt (trivial or mild residual shunt: 5.4%; moderate residual shunt: 1.7%). The presence of a residual shunt or its severity was not associated with the primary or secondary endpoints.

The mean RoPE score in our cohort was 6.10 ± 1.79 (median: 6.0), and 43.2% of patients presented a score of > 6. Table II details the clinical outcomes of the full cohort and both groups based on the severity of RoPE score.

The primary clinical endpoint occurred in 23 (5.8%) patients (stroke: 4.8%; TIA: 1.0%) during the follow-up. Univariate Cox regression analysis (Table III) revealed current smoker status, concomitant presence of coronary disease; TIA, transient ischemic attack; CAD, coronary artery disease; TEE, tranesophageal echocardiography; IASA, interatrial septal aneurysm; LA, left atria; and PFO, patent foramen ovale.

**Table II.** Primary and Secondary Endpoints of Total Cohort and Low and High RoPE Score Groups

| All-cause mortality (\( n/\% \)) | 8 (2.0) | 0 (0.0) | 8 (3.6) | 0.011 |
| Cardiac mortality (\( n/\% \))   | 2 (0.5) | 0 (0.0) | 2 (0.9) | 0.50  |
| Neurologic mortality (\( n/\% \))| 4 (1.0) | 0 (0.0) | 4 (1.8) | 0.13  |
| Ischemic events (\( n/\% \))     | 23 (5.8) | 2 (1.2) | 21 (9.4) | 0.001  |
| Stroke (\( n/\% \))              | 19 (4.8) | 2 (1.2) | 17 (7.6) | 0.003  |
| TIA (\( n/\% \))                 | 4 (1.0) | 0 (0.0) | 4 (1.8) | 0.13  |
| Atrial fibrillation (\( n/\% \)) | 17 (4.3) | 2 (1.2) | 15 (6.8) | 0.006  |

RoPE indicates Risk of Paradoxical Embolism score; and TIA, transient ischemic attack.
artery disease, lower RoPE score, and higher left atrial dimensions as predictors of recurrent ischemic cerebrovascular events in our cohort. Therefore, these significant variables were included in the multivariate Cox regression (forward selection) analysis. The resultant model revealed that only lower RoPE score and presence of coronary artery disease were independent predictors of the primary endpoint. Hence, in this cohort, a RoPE score of ≤ 6 proved to be independently associated with stroke or TIA recurrence after percutaneous closure of PFO (Figure).
Secondary endpoints were less frequent in our cohort, with an all-cause mortality rate of 2.0% (8 patients) during follow-up: 4 (1.0%) patients died of stroke, 2 (0.5%) died of myocardial infarction, and 2 (0.5%) died of non-cardiac and non-neurological causes. A statistically significant correlation was verified between all-cause mortality and the RoPE score ($r = -0.127, P = 0.012$), as all deaths occurred in the low RoPE score group (score: ≤ 6). The predictors of all-cause mortality were not searched because of low event rate. NOAF was significantly more common in the low RoPE score group (6.8% versus 1.2%, $P = 0.006$). There was no correlation between NOAF and device types, presence of residual shunt, or its severity.

Discussion

The present study reports the use of the RoPE score to independently predict the recurrence of cerebrovascular events after percutaneous PFO closure. Patients with a lower score (≤ 6) are at a higher risk of recurrence during follow-up.

Three randomized clinical trials (RESPECT, CLOSURE I, and PC) that were performed to compare percutaneous PFO closure with medical therapy alone did not reveal the expected superiority for this invasive technique in the intention-to-treat analysis.\textsuperscript{6-11} Low rate of recurrence of ischemic events, short follow-up period, and inappropriate patient selection have been suggested to explain the non-superiority effect of percutaneous PFO closure in these trials.\textsuperscript{16} Recently, the extended 10-year follow-up results of the RESPECT trial showed that patients who underwent PFO closure had a statistically significant 54% relative risk reduction of recurrent cryptogenic stroke compared with those assigned to medical therapy, supporting the hypothesis of the procedure’s long-term benefit.\textsuperscript{19}

To overcome the difficulty of differentiating an ischemic event related to the PFO from an ischemic event from other cause with an incidental PFO, Kent, et al. conducted the RoPE study.

Our study applied the RoPE score in a young population, with a mean age of 44.7 years, with one or more ischemic events to which a secondary prevention strategy, by percutaneous closure of PFO, was chosen based on a clinical comprehensive evaluation. We report a 97% immediate success rate and a low rate of procedure complications, which substantiates the efficacy and safety of the procedure.

The population’s mean age was in light with the previous randomized clinical trials,\textsuperscript{5-11} nonetheless, the important prevalence of cardiovascular risk factors, notably, dyslipidemia, hypertension, or smoking status, led to a higher proportion of patients (56.8%) presenting with a lower RoPE score (≤ 6). The technical procedure characteristics were not different between the 2 groups.

During the follow-up, a 5.8% rate of ischemic cerebrovascular event recurrence and a 2.0% all-cause mortality rate were reported. Both the ischemic cerebrovascular event recurrence and the mortality events were significantly more frequent in the lower RoPE score group, representing older patients and with more comorbidities.

Smoker status, concomitant coronary artery disease, and lower RoPE score were predictors of ischemic cerebrovascular event recurrence in univariate analysis, but only a lower RoPE score and coronary artery disease remained independent predictors in multivariate analysis, possibly reflecting the inclusion of smoking status variable in the score calculation. These predictors represent indirect markers of the atherosclerotic process and these new cerebrovascular events probably have an atherosclerotic origin and cannot be prevented by strategies targeting the PFO. A lower RoPE score was statistically associated with a higher rate of stroke and recurrence of TIA, and patients presenting a score of ≤ 6 showed a 5.55 increased risk of adverse event recurrence in the multivariate model. Other primary and secondary prevention strategies are necessary for patients with lower RoPE scores, once they remain at increased risk of ischemic event recurrence, despite PFO closure. There were only 2 ischemic events in the group with RoPE score > 6, showing that this score differentiates this population risk of ischemic event recurrence.

The low mortality rate reported in our study does not allow an unquestionable determination of independent predictors; nonetheless, a significant correlation was noticed between higher mortality rate and a lower RoPE score. There were no deaths in the higher RoPE score group.

The NOAF during the follow-up was significantly more common in the lower RoPE score group, and a higher left atrial size was found to be a predictor of adverse event recurrence in univariate analysis. Nonetheless, after adjusting for other significant variables, neither the left atrial diameter nor the diagnosis of NOAF remained predictors of ischemic cerebrovascular event recurrence.

The presence of interatrial septal aneurysm has been associated with a higher risk of ischemic cerebrovascular event recurrence in previous studies;\textsuperscript{22} however, that hypothesis was not observed in our study. Also, the procedure characteristics such as the type of device and the presence or severity of residual shunt were not predictors of adverse outcomes.

**Study limitations:** We had 8 patients lost to follow-up during the study. Moreover, despite a mean follow-up period of 6.4 years, the low mortality rate did not allow a logistic regression analysis to test if the RoPE score could predict this major adverse event. It remains a challenge to accurately state the cause of the recurrent cerebrovascular ischemic events. An atherosclerotic origin seems to be the most likely cause since no association with residual shunt, device type, or NOAF was established, although other causes might be revealed with longer follow-up duration.

**Conclusion**

RoPE score was shown to be an independent predictor of recurrent ischemic cerebrovascular events and a score of ≤ 6 identifies patients with a significantly higher risk. Percutaneous closure of PFO is an important tool for secondary prevention after a cryptogenic stroke, especially in the younger population without the classical cardiovascular risk factors. In our experience, it is a safe and effective procedure, with a low rate of complications and excellent clinical results.
Our study reinforces the importance of improving patient selection for this procedure, in order to provide this treatment to those who will benefit from it, considering that the best strategy for secondary prevention of stroke is still an open question. Patients with a RoPE score of ≤ 6 should be followed up carefully and be targeted for other secondary prevention strategies that address their classical cardiovascular risk factors and NOAF, to prevent the occurrence of further ischemic cerebrovascular events from other causes. Patients with a higher RoPE score presented with a very low rate of recurrent ischemic cerebrovascular events and no mortality during long-term follow-up, possibly reflecting the beneficial effect of PFO closure in this cohort.

Disclosures

Conflicts of interest: There are no conflicts of interests to declare.

References