Title

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CHAPTER

4

Definition of Cryptogenic Stroke, the RoPE Score, and Assessment of Embolic Stroke of Undetermined Source

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OUTLINE

INTRODUCTION

The prevalence of patent foramen ovale (PFO) in the general population is approximately 25%, but 40%–60% of patients with cryptogenic stroke are found to have a PFO [1]. This increased frequency of PFO in cryptogenic stroke suggested that PFO could have an etiological role in some cryptogenic strokes. However, the initial randomized clinical trials that evaluated the efficacy and safety of percutaneous PFO closure for the prevention of recurrent cryptogenic stroke (2012 CLOSURE I, 2013 PC trial, and 2013 RESPECT) could not demonstrate, with statistical significance, that PFO closure was superior to medical therapy in an intention-to-treat analysis [2–4]. These earlier randomized trials of PFO closure for cryptogenic stroke are discussed in detail in Chapter 6. Yet, an unequivocal benefit of PFO closure in patients with cryptogenic stroke was documented in 2017–18, when subsequent randomized trial reports (2017 Long-Term RESPECT, 2017 REDUCE, 2017 CLOSE, and 2018 DEFENSE-PFO) demonstrated superiority of PFO closure over standard of care medical therapy (Chapter 7) [5–8]. Although most neurologists conceded that at least a portion of cryptogenic strokes were due to PFO functioning as a pathway for a paradoxical embolus to reach the brain, the neurologic and cardiologic societies took a conservative approach and warned against mechanical PFO closure as an advisable therapy after a cryptogenic stroke [9]. The guidelines did not acknowledge that the early trials demonstrated noninferiority of PFO closure compared with medical therapy.

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Moreover, since paradoxical embolism was treated as a diagnosis of exclusion, all other known causes of stroke had to be evaluated and rejected before it was concluded that the PFO was causally related to the stroke. Thus, the diagnosis of paradoxical embolism was met with overzealous skepticism, with many influential neurologists claiming that the PFO was just an "innocent bystander" that had no relation to the index stroke, and therefore, should not be closed. Articles discussed the likelihood that hitherto undetected paroxysmal atrial fibrillation (AF) would be a more likely etiology for the cryptogenic stroke, and therefore, should be investigated with more stringent rhythm monitoring, including placement of subcutaneous cardiac monitors for several months [10,11]. There are no studies comparing the likelihood that a systemic embolism is due to AF associated with different anatomical variables versus PFO with different anatomical variables.

Other potential mechanisms of stroke may be present in patients even if they indeed had a PFO-related stroke, including lacunar disease, hypercoagulable states, and aortic or carotid atheroma with the potential for embolism. One system commonly used to categorize the etiology of stroke is the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification, which, on the basis of clinical features and results of diagnostic studies, such as brain imaging with computed tomography (CT) or magnetic resonance (MR), cardiac imaging (echocardiography), Doppler imaging of extracranial arteries, arteriography, and laboratory assessments for a prothrombotic state, denotes 5 subtypes of ischemic stroke: (1) large-artery atherosclerosis, (2) cardioembolism, (3) small-artery occlusion (e.g., lacunar infarct), (4) stroke of other determined etiology, and (5) stroke of undetermined etiology (i.e., cryptogenic stroke) [12]. Of note, the TOAST classification does not recognize paradoxical embolism mediated by a right-to-left shunt (i.e., PFO, atrial septal defect, or pulmonary arteriovenous malformation) as a culprit of stroke in any of the first 4 categories. Similarly, there is no recognition of paroxysmal AF even though persistent AF is characterized as cardioembolism. This implies that both the subgroups of stroke patients with a right-to-left shunt and those with paroxysmal AF would fall under the category of "stroke of undetermined etiology" (i.e., cryptogenic stroke) under the TOAST classification.

The EMBRACE (30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event) trial randomized patients with cryptogenic stroke to a standard of care 24-hour cardiac monitor or 30-day event-triggered loop recorder to assess for occult AF. It found a significantly higher prevalence of paroxysmal AF in the cryptogenic stroke patients monitored for 30 days versus those monitored for only 24 hours after stroke (16.1% vs. 3.2%, 95% CI 8.0−17.6, $P < .001$) [10]. This finding emphasized the importance of long-term cardiac monitoring to assess for the presence of paroxysmal AF in cryptogenic stroke patients and, if present, initiating appropriate anticoagulation for the prevention of recurrent stroke. The EMBRACE study was interpreted by some people as further evidence that PFO was unlikely to be causally related to stroke, and it should, therefore, not be treated with percutaneous closure. Of note, AF has no impact on the risk of a PFO to mediate paradoxical embolism, and the average age of patients in the EMBRACE trial was 72.5 years, an elderly patient population expected to have a higher prevalence of AF, as compared to the younger (age $\leq$60 years) cryptogenic stroke patients enrolled in the PFO closure trials.

To address the quandary of when to consider PFO as the guilty offender and when to exclude it as an innocent bystander, the RoPE (Risk of Paradoxical Embolism) study was designed to assist physicians in making the appropriate diagnosis [13,14].

THE RoPE STUDY

In 2013, the RoPE (Risk of Paradoxical Embolism) study, an international collaboration led by David Kent and David Thaler of Tufts University, provided a series of mathematical models that could be used to (1) stratify patients by the conditional probability that an index cryptogenic stroke was PFO-related and (2) predict the likelihood that a stroke would recur [13,14].

The objective of the first mathematical model was to estimate the patient-specific probability that a PFO was pathogenically related to the index stroke by determining the "PFO propensity." This was achieved by constructing a database of patients with cryptogenic stroke, both with and without PFO, by combining existing cohort studies, and reviewing the patient characteristics. A database was built consisting of cryptogenic stroke subjects with PFO (n = 1274) and without PFO (n = 1749) based on 12 different cohort studies [15]. Table 4.1 lists the clinical, echocardiographic, and radiological variables of interest. An atrial septal aneurysm (ASA) was defined as a hypermobile interatrial septum that resulted in an excursion of at least 10 mm from the midline plane of the septum into either the right or left atrium with each heartbeat. Of note, while ASA occurs in 2.2% of the general population, it occurs in approximately 20%−45% of patients with PFO [16,17]. This underlines the plausible hypothesis that an ASA prevents fusion

TABLE 4.1 Initial Clinical, Echocardiographic, and Radiological Variables of Interest in Cryptogenic Stroke Patients With PFO (Adapted from [13]).

Variable Type	Variable
Clinical	Age
	Gender
	Race
	History of the following (prior to index stroke)
	Migraines
	Hypertension
	Diabetes
	Prior cerebral ischemia
	Coronary artery disease
	Obesity
	Hypercholesterolemia
	Smoking status
	Antithrombotic medications
	Deep vein thrombosis
	Pulmonary embolism
	Hypercoagulable states
	Antithrombotic medications after index event
	National Institutes of Health Stroke Severity Score
Echocardiographic	Hypermobility of interatrial septum (ASA)
	Interatrial shunting at rest (not during Valsalva maneuver)
	Volume of interatrial shunt (maximum number of bubbles in left atrium)
	Anatomical PFO size
	Spontaneous Doppler flow seen on color
Radiological	CT/MR imaging of cerebral infarct at time of index stroke (yes/no)
	Number of prior cerebral infarcts
	Anatomical location of index and prior infarct(s)

ASA, atrial septal aneurysm; *CT*, computed tomography; *MR*, magnetic resonance; *PFO*, patent foramen ovale.

of the septum secundum with the septum primum and thus predisposes to the presence of a PFO. The physiological shunt size of a PFO was determined by the number of bubbles that cross the PFO on transesophageal echocardiography, with large shunts defined as the appearance of $\geq$20 microbubbles in the left atrium after an agitated saline injection. Table 4.2 summarizes the characteristics of cryptogenic stroke patients with and without PFO. Although sex distribution was similar between the 2 groups, cryptogenic stroke patients with PFO were considerably younger and less likely to have conventional risk factors of atherosclerosis (e.g., diabetes, coronary artery disease, hypertension, hypercholesterolemia, smoking, or history of cerebrovascular events) compared to cryptogenic stroke patients without PFO. On neuroimaging, cryptogenic stroke patients with PFO had fewer findings of prior stroke, and the infarcts were more likely to be large ($>$1$-$1.5 cm) and superficial, compared to stroke patients without PFO.

The objective of the second mathematical model was to estimate the patient-specific risk of stroke recurrence. This was achieved by analyzing the clinical, radiographic, and echocardiographic characteristics of patients with both a cryptogenic stroke and PFO.

The objective of the third mathematical model was to create a composite index based on the patient-specific PFO propensity (model 1) and patient-specific stroke recurrence risk (model 2). This was achieved by combining both

TABLE 4.2 Comparison of Cryptogenic Stroke Patient Characteristics With and Without PFO.

	PFO (n = 1274)	Non-PFO (n = 1749)	*P* Value
PATIENT CHARACTERISTICS			
Male	58.9 (751/1274)	59.3 (1038/1749)	.82
Age >65 y	21.5 (274/1274)	35.9 (627/1748)	<.0001
White	86.1 (515/598)	79.3 (649/818)	.0010
Diabetes	8.9 (113/1269)	18.6 (325/1746)	<.0001
Coronary artery disease	6.7 (67/1005)	12.0 (172/1434)	<.00001
Hypertension	32.7 (415/1271)	53.2 (927/1744)	<.0001
Hypercholesterolemia	22.5 (195/866)	30.6 (425/1387)	<.0001
Current smoker	32.5 (410/1263)	36.0 (622/1727)	.04
History of stroke/TIA	11.9 (151/1270)	18.0 (314/1740)	<.0001
RADIOLOGIC VARIABLES			
Prior stroke, % yes	22.6 (196/867)	31.1 (396/1272)	<.0001
Number of lesions	n = 901	n = 1261	.32
Multiple	13.3 (120)	12.5 (158)	
Not multiple	72.5 (653)	75.2 (948)	
TIA	14.2 (128)	12.3 (155)	
Size	n = 930	n = 1324	.02
Large	59.1 (550)	55.9 (740)	
Not large	27.1 (252)	32.4 (429)	
TIA	13.8 (128)	11.7 (155)	
Location	n = 907	n = 1173	<.0001
Superficial	54.1 (491)	44.9 (527)	
Deep	31.8 (288)	41.9 (491)	
TIA	14.1 (128)	13.2 (155)	

PFO, patent foramen ovale; *TIA*, transient ischemic attack.
Adapted with permission from Ref. [14].

models. The composite index was then applied to the completed clinical trials that compared percutaneous PFO closure with medical therapy to stratify patients based on clinical benefit from device closure. Fig. 4.1 summarizes the RoPE study.

A multivariate regression model was performed on each of the variables listed in Table 4.1 to predict the respective odds ratio (OR). Table 4.3 lists any clinical or radiographic variable with an OR of <1 and a *P*-value < .05. Since the original objective of the RoPE study was to develop a mathematical model that predicted the presence of PFO in someone presenting with cryptogenic stroke, echocardiographic variables, despite being relevant, were ultimately excluded. Based on the similarity of the OR of each variable, the RoPE score was derived, which is outlined in Table 4.4. Points are assigned based on the decade of life (5 points for those in their 20s, 4 points for those in their 30s, down to 1 point for those in their 60s), and a single point is assigned for the absence of each of the 3 vascular risk factors (diabetes, hypertension, smoking), the lack of a prior stroke or transient ischemic attack, and the presence of a cortical stroke on brain imaging. A cryptogenic stroke patient <30 years old with no hypertension, diabetes, history of stroke, or transient ischemic attack, who is a nonsmoker and has a cortical infarct (i.e., young, without conventional vascular risk factors, and with a superficial infarct) will earn 10 points, the maximum score possible. On the other hand, a cryptogenic stroke patient ≥70 years old with hypertension, diabetes, prior stroke, who is a current smoker and has a subcortical infarct (i.e., older, multiple conventional vascular risk factors, and with a deep infarct)

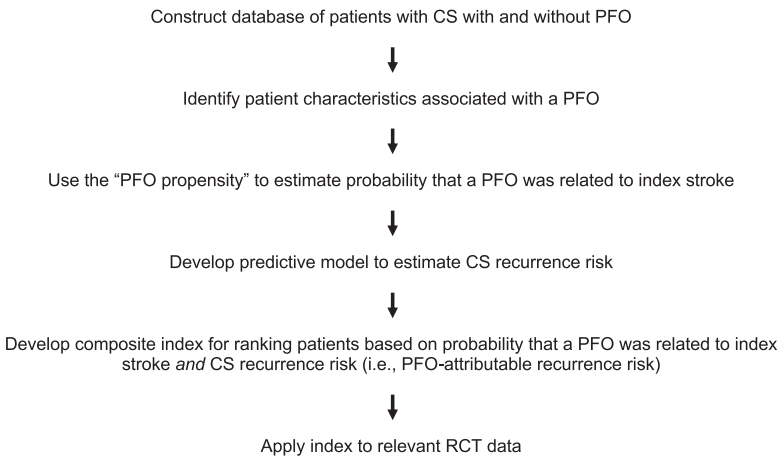

FIGURE 4.1 Summary of the RoPE study. *CS*, cryptogenic stroke; *PFO*, patent foramen ovale; *RCT*, randomized controlled Trial (Adapted from [13]).

TABLE 4.3 Multivariate Regression Model Predicting Presence of PFO.

	OR (95% CI)	*P* Value
Age, per 10-year increase	0.72 (0.67–0.77)	<.0001
Diabetes	0.62 (0.51–0.83)	.0006
Hypertension	0.68 (0.57–0.81)	<.0001
Current smoker	0.60 (0.50–0.71)	<.0001
History of stroke or TIA	0.78 (0.62–0.99)	.04
Radiology, deep (vs. superficial)	0.68 (0.54–0.84)	.0006

OR, odds ratio; *PFO*, patent foramen ovale; *TIA*, transient ischemic attack.
Adapted with permission from Ref. [14].

will earn 0 points, the minimum score possible. When this scoring system was applied retrospectively to the various studies responsible for creating the series of mathematical models, the PFO prevalence not only matched the background population (23% for RoPE score 0–3) but also positively correlated with the RoPE score, having a very high PFO prevalence of 73% for RoPE scores 9–10 (Table 4.5).

The likelihood that the PFO was the cause of the cryptogenic stroke, also known as the PFO-attributable fraction, was estimated using Bayes theorem with a control PFO frequency of 25%; this specific percentage was chosen because it was the average prevalence seen across several adult autopsy studies. This yielded a PFO-attributable fraction ranging from 0% to 88%. The higher the RoPE score, the higher the PFO-attributable fraction, consistent with the pattern seen when applying the score retrospectively to the studies responsible for creation of the overall model (Table 4.6).

When the RoPE score was applied retrospectively to the early randomized trials of PFO closure for stroke (2012 CLOSURE I, 2013 PC trial, and 2013 RESPECT), the investigators found that subjects with a wide range of RoPE scores were included in the randomized trials (but not as wide a range as in the RoPE study). The study authors concluded that patients with non-PFO-related cryptogenic stroke would presumably not have benefitted from PFO closure, and the statistically nonsignificant results may have been due to inclusion of patients who were unlikely to show a benefit rather than a failure of treatment per se [18].

In the RoPE study, the 2-year rate of recurrent stroke or transient ischemic attack in cryptogenic stroke patients with PFO was estimated using the Kaplan–Meier survival analysis (Table 4.7). The data show that recurrence rates decrease as the RoPE score increases, suggesting that patients with cryptogenic stroke most likely due to PFO (i.e., high PFO-attributable fraction) are least likely to experience recurrent ischemic events within a short period of time compared with strokes from other occult mechanisms like undetected paroxysmal AF or substenotic atherosclerosis. We now know from the longer-term PFO randomized trials that the recurrent stroke rate on medical therapy is 1% per year.

TABLE 4.4 RoPE Score Calculator.

Characteristic	Points	RoPE Score
No history of hypertension	1	
No history of diabetes	1	
No history of stroke or TIA	1	
Nonsmoker	1	
Cortical infarct on imaging	1	
Age, years		
18–29	5	
30–39	4	
40–49	3	
50–59	2	
60–69	1	
≥70	0	
Total score (sum of individual points)		
Maximum score (a patient <30 years with no hypertension, no diabetes, no history of stroke or TIA, nonsmoker, and cortical infarct)		10
Minimum score (a patient ≥70 years with hypertension, diabetes, prior stroke, current smoker, and no cortical infarct)		0

RoPE, Risk of Paradoxical Embolism; *TIA*, transient ischemic attack.
Adapted with permission from Ref. [14]

The RoPE score gives clinicians a tool to predict the probability that a discovered PFO in a patient with cryptogenic stroke may be causally related to the stroke. The main strength of the RoPE score is the ease of obtaining the clinical characteristics that constitute the score. A major weakness of the RoPE score is the exclusion of several variables that may point to a PFO as the stroke mediator (e.g., high-risk PFO anatomy, history of deep venous thrombosis [DVT] or pulmonary embolism [PE], obesity as a predilection for venous thrombosis, hypercoagulable state, prolonged travel or forced immobility, migraine with aura, or Valsalva at stroke onset) due to inconsistent data collection across the various databases used to create the scoring system. Ozdemir et al. compared clinical, coagulation, and biochemical parameters in cryptogenic stroke patients who had transesophageal echocardiography (TEE)-confirmed PFO (n = 89) versus cryptogenic stroke patients without PFO (n = 86) using the Stroke Prevention and

TABLE 4.5 PFO Prevalence (Confirmed by TCD/TEE) in Cryptogenic Stroke Patients by RoPE Score Using Control Rate of 25%.

Cryptogenic Stroke Patients (n = 3023)		
RoPE Score	**No. of Patients**	**PFO Prevalence, % (95% CI)**
0–3	613	23 (19–26)
4	511	35 (31–39)
5	516	34 (30–38)
6	482	47 (42–51)
7	434	54 (49–59)
8	287	67 (62–73)
9–10	180	73 (66–79)

PFO, patent foramen ovale; *RoPE*, Risk of Paradoxical Embolism; *TCD*, transcranial Doppler; *TEE*, transesophageal echocardiography.
Adapted with permission from Ref. [14].

TABLE 4.6 PFO-Attributable Fraction in Cryptogenic Stroke Patients by RoPE Score Using Control Rate of 25% and Bayes Theorem.

Cryptogenic Stroke Patients (n = 3023)		
RoPE Score	**No. of Patients**	**PFO-Attributable Fraction, % (95% CI)**
0–3	613	0 (0–4)
4	511	38 (25–48)
5	516	34 (21–45)
6	482	62 (54–68)
7	434	72 (66–76)
8	287	84 (79–87)
9–10	180	88 (83–91)

PFO, patent foramen ovale; *RoPE*, Risk of Paradoxical Embolism.
Adapted with permission from Ref. [14].

TABLE 4.7 2-Year Stroke/TIA Recurrence Rate by RoPE Score Using Control Rate of 25% and Kaplan–Meier Survival Analysis.

Cryptogenic Stroke Patients with PFO (n = 1324)		
RoPE Score	**No. of Cryptogenic Stroke Patients with PFO**	**Estimated 2-y Stroke/TIA Recurrence Rate (Kaplan–Meier), % (95% CI)**
0–3	108	20 (12–28)
4	148	12 (6–18)
5	186	7 (3–11)
6	236	8 (4–12)
7	263	6 (2–10)
8	233	6 (2–10)
9–10	150	2 (0–4)

PFO, patent foramen ovale; *RoPE*, Risk of Paradoxical Embolism; *TIA*, transient ischemic attack.
Adapted with permission from Ref. [14].

Atherosclerosis Research Centre (SPARC) database in London, Ontario. Following multivariate logistic regression modeling, a history of DVT or PE (OR 4.39, 95% CI 1.23–15.69, $P = .023$), prolonged travel (OR 8.77, 95% CI 1.775–43.3, $P = .008$), migraine (OR 2.30, 95% CI 1.07–4.92, $P = .031$), a Valsalva maneuver preceding the onset of focal neurological symptoms (OR 3.33, 95% CI 1.15–9.64, $P = .026$), and waking up with stroke or transient ischemic attack (OR 4.53, 95% CI 1.26–16.2, $P = .018$) were independently associated with PFO-associated cerebrovascular events [19].

RoPE SCORE VALIDATION

Prefasi et al. attempted to validate the RoPE score in a cohort of cryptogenic stroke patients ≤50 years old and identify the cutoff point with the highest likelihood that PFO is related to stroke. The investigators recruited cryptogenic stroke patients from 2007 to 2013. A receiver operating characteristic curve was performed to identify the RoPE score with the highest sensitivity and specificity to detect the presence of a PFO. The study included 58 cryptogenic stroke patients aged ≤50 years. No patient had a RoPE score of 0–3; 8 patients (14%) had a RoPE score of 4–5; 11 patients (19%) had a RoPE score of 6; 11 patients (19%) had a RoPE score of 7; and 28 patients (48%) had

TABLE 4.8 PFO-Attributable Fraction in Cryptogenic Stroke Patients ≤50 Years Old by RoPE Score Using Bayes Theorem (Adapted from [20]).

Cryptogenic Stroke Patients ≤50 years Old (n = 58)			
RoPE Score	**Number of Cases**	**PFO Prevalence, % (95% CI)**	**PFO-Attributable Fraction, % (95% CI)**
0–3	0	–	–
4–5	8	12.5 (0.31–52.6)	0 (0–69.9)
6	11	0 (0–28.5)	0 (0–16.3)
7	11	18.1 (2.2–51.8)	0 (0–68.9)
8–10	28	53.6 (33.9–72.5)	71.1 (35–87.3)
≤7	30	10 (2.1–26.5)	0 (0–7.5)
>7	28	53.6 (33.9–72.5)	71.1 (35–87.3)

PFO, patent foramen ovale; *RoPE*, Risk of Paradoxical Embolism.

a RoPE score of 8–10. The identified cutoff point was 7, with a sensitivity of 69.4% and specificity of 62.5%. Cryptogenic stroke patients with a RoPE score ≤7 had a low PFO prevalence of 10% and a PFO-attributable fraction of 0% (Table 4.8) [20].

On the contrary, Boon et al. investigated 126 patients, aged 26–69 years, presenting for a TTE bubble study as part of their cryptogenic stroke workup. They found that, assuming a PFO prevalence of 25% in the general population, the PFO-attributable risk for RoPE score ≤6 was 67% compared to 70% for a RoPE ≥7 ($P = .76$) [21]. This shows that there can be significant attributable risk even in patients with low RoPE scores, thereby highlighting the initial description in the paper of Kent et al. that a very low RoPE score does not rule out a PFO-related stroke or contraindicate PFO closure.

RoPE SCORE ADJUSTED FOR ANATOMICAL–FUNCTIONAL PFO FEATURES

The RoPE score is based on clinical criteria and it does not include any anatomical or functional characteristics, such as persistent shunt at rest or large right-to-left shunt, presence of ASA, or a long-tunneled PFO. Goel et al. reviewed TEE data to compare the PFO morphology in 58 patients who had PFO closure for cryptogenic stroke with 58 asymptomatic patients with PFO found incidentally [17]. The data were analyzed for differences in PFO size (defined as maximum separation of the septum primum and septum secundum on TEE), tunnel length (defined as maximum overlap of the septum primum and septum secundum), presence of atrial septal aneurysm (defined as >11 mm mobility), shunt severity (mild, 3 to 9 microbubbles; moderate, 10 to 30 microbubbles; severe, >30 microbubbles), prominence of the Eustachian valve, and presence of a Chiari network. Patients with cryptogenic stroke had larger PFOs (3.9 ± 1.6 vs. 2.9 ± 1.4 mm, $P < .001$), longer tunnels (14 ± 6 vs. 12 ± 6 mm, $P = .05$), a greater frequency of ASA (45% vs. 21%, $P < .005$), and greater proportion of severe shunting (16% vs. 5%, $P < .06$) compared with controls. The frequencies of a prominent Eustachian valve or Chiari network were not significantly different when compared with controls. Thus, it is reasonable to consider including certain anatomical PFO features when evaluating patients with cryptogenic stroke and a PFO to help delineate pathogenic PFOs from incidental PFOs.

Rigatelli et al. assessed the potential role of a modified anatomical–functional RoPE (AF-RoPE) score in guiding selection of patients with cryptogenic stroke for device closure or medical therapy [22]. The investigators reviewed the data of 1040 patients (mean age 47.3 ± 17.1 years, 68% females) prospectively enrolled in 2 different Italian registries over a 13-year period to select both anatomical and functional parameters that could be incorporated into a modified RoPE score. Multiple stepwise logistic regression analyses of anatomical and functional variables demonstrated that persistent right-to-left shunt at rest (OR 5.9, 95% CI 1.8–11.0, $P < .001$), ASA types 3–5 per Olivares-Reyes et al. classification (OR 3.9, 95% CI 0.5–8.0, $P < .001$), a tunnel-like PFO (OR 3.5, 95% CI 0.8–6.0, $P < .001$), and large curtain right-to-left shunt on transcranial Doppler (OR 1.9, 95% CI 0.3–4.0, $P < .001$) conferred the highest risk of recurrent stroke. This resulted in the creation of the AF-RoPE score (Table 4.9). Of the echocardiographic features that influence recurrence, as shown by the PFO-ASA study by Lamy et al. in 2002 [14], a floppy

TABLE 4.9 AF-RoPE Score Calculator (Adapted from [22]).

Characteristic	Points	RoPE Score
No history of hypertension	1	
No history of diabetes	1	
No history of stroke or TIA	1	
Nonsmoker	1	
Cortical infarct on imaging	1	
Curtain R-L shunt	1	
Persistent R-L shunt at rest	2	
ASA types 3 - 5	2	
Tunnel-like PFO	2	
Age, years		
18–29	5	
30–39	4	
40–49	3	
50–59	2	
60–69	1	
≥70	0	

AF-RoPE, anatomical–functional Risk of Paradoxical Embolism; *ASA*, atrial septal aneurysm; *PFO*, patent foramen ovale; *R-L*, right-to-left; *TIA*, transient ischemic attack.

septum together with a PFO increased the risk of recurrence significantly, with an adjusted hazard ratio of 2.31 (95% CI 1.05–5.05).

Surprisingly, in the RoPE cohort, shunt size was related to recurrence risk but in a direction contrary to what was predicted (i.e., patients with small shunts were 3.26 [95% CI 1.59–6.67] times more likely to have a recurrent stroke or transient ischemic attack than those with large shunts). The study authors' explanation for this observation was that patients with small shunts have PFOs that are more often closed with small amounts of stagnant blood within the tunnel, in turn increasing the risk of thrombus formation in situ. Although this hypothesis has often been repeated, there are no data that demonstrate that blood within a PFO is stagnant, or that blood within a PFO forms a thrombus in situ. The counterargument comes from interventional operators who have yet to report a stroke induced by passing guidewires and catheters across a PFO.

In a subsequent study conducted by the AF-RoPE investigators, the AF-RoPE score and the standard RoPE score were applied in a prospective and blinded fashion to a cohort of 406 patients (mean age 43.6 ± 17.0 years) referred for management of cryptogenic stroke and PFO over a 3-year period from February 2013 to February 2016. Patients with an AF-RoPE score >11 had increased stroke recurrence and abnormal cerebral neuroimaging. The AF-RoPE score resulted in a more precise separation of patients with stroke and PFO, implying that anatomic and functional characteristics of a given PFO can better guide the selection of patients for PFO closure.

Of note, the more recent randomized trials of PFO closure for stroke showed that percutaneous PFO closure performed for patients with cryptogenic stroke who have an ASA or a large PFO may receive greater benefit from device closure, having the lowest number needed to treat [5,6,8,23] (Chapter 7). However, this observation was not made within a single trial. Rather, it was a comparison between trials. A consistent differential treatment effect for subgroups of patients with different PFO characteristics has not been established yet.

EMBOLIC STROKE OF UNDETERMINED SOURCE

More recently, the term embolic stroke of undetermined source (ESUS) has been recommended [24]. During the 1990s and 2000s, the high incidence and lack of progress in developing an optimal prophylactic regimen for

secondary prevention of cryptogenic strokes convinced many experts to change the way trials should approach recurrent cryptogenic stroke prevention. Although a major risk factor (e.g., atherosclerosis, AF or arteritis) is often identified in nonlacunar ischemic strokes, 25% of these strokes remain without an obvious cause despite extensive workup. The TOAST classification labeled these strokes as cryptogenic (i.e., of unknown cause). Hart el al. proposed that these strokes should instead be called ESUS, arguing that most of these strokes are embolic in etiology, and this recognition is more clinically useful than the vague term cryptogenic stroke. Of note, ESUS recognizes ischemic stroke due to paroxysmal AF as a separate entity but not ischemic stroke due to right-to-left shunt, such as a PFO, thereby yielding some but incomplete improvement over the term cryptogenic. Regardless, the definition of cryptogenic stroke used in the PFO closure trials was more or less similar to the more recently proposed ESUS classification.

Since the introduction of the term ESUS, several randomized trials have been initiated that compared anticoagulants to antiplatelet therapy in reducing the risk of recurrent ESUS, one of which is still ongoing Apixaban for Treatment of Embolic Stroke of Undetermined Source (ATTICUS). In the NAVIGATE ESUS (Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source) trial, Hart et al. compared the efficacy and safety of rivaroxaban with acetylsalicylic acid for the prevention of recurrent stroke in patients with ESUS [25]. The primary efficacy endpoint, defined as the first recurrence of ischemic or hemorrhagic stroke or systemic embolism, occurred in 4.8% (172/3609) of patients in the rivaroxaban arm and in 4.4% (160/3604) of patients in the acetylsalicylic acid arm (HR 1.07, 95% CI 0.87−1.33, $P = .52$). The primary safety outcome, defined as the rate of major bleeding, occurred in 1.7% (62/3609) of patients on rivaroxaban and 0.6% (23/3604) of patients on acetylsalicylic acid (HR 2.72, 95% CI 1.68−4.39, $P < .001$). Thus, rivaroxaban was not significantly superior to acetylsalicylic acid in preventing recurrent stroke after an initial ESUS and was associated with a higher risk of bleeding. In the 5390-patient RE-SPECT ESUS (Dabigatran Etexilate for Secondary Stroke Prevention in Patients with Embolic Stroke of Undetermined Stroke) trial, whose results have been presented but not officially published yet, investigators looked at the efficacy and safety of dabigatran against acetylsalicylic acid for the prevention of recurrent stroke in patients with ESUS. The primary efficacy endpoint, defined as the time to first recurrent stroke, was 4.1% per year with dabigatran and 4.8% per year with acetylsalicylic acid over a mean follow-up of 19 months (HR 0.85, $P = .1$) [26]. The rate of major bleeding was similar in both arms (1.7% per year with dabigatran and 1.4% per year with acetylsalicylic acid). Thus, dabigatran was also not significantly superior to acetylsalicylic acid in preventing recurrent stroke after an initial ESUS. Publication of the ongoing and completed trials will provide more insight on the role of anticoagulants, if any, in ESUS patients who have a PFO.

CONCLUSION

Using the RoPE score, Kent and Thaler et al. presented a simple system that can help to identify whether a PFO in a patient with cryptogenic stroke may be causally related to that stroke. Given the strength and consistency of each variable included within the RoPE score, the calculated score allows clinicians to identify cryptogenic stroke patients with PFO who will benefit most from PFO-specific therapy, thereby allowing for the proper use of finite resources and avoiding unnecessary interventions. However, cryptogenic stroke patients who have a PFO should be evaluated as a whole, since a detailed history, physical examination, and echocardiography may identify risk factors that are not considered by the RoPE score. Treating physicians should also be cautioned not to fall into the conjecture that a PFO cannot cause a stroke in the presence of another stroke etiology, as this assumption is counterintuitive and not implemented with any other medical condition. For instance, if an ischemic stroke patient has both AF and carotid artery disease, we do not treat one condition and ignore the other.

The neurologist who makes the diagnosis of a PFO-associated cryptogenic stroke has the RoPE criteria methodically in mind, even if a specific RoPE score is not calculated. It is important to note that despite a RoPE score, low or high, clinical judgment needs to be applied. We have all seen young vasculopaths with strokes, making the underlying atherosclerosis a more likely mechanism than a PFO despite the high RoPE score. On the other hand, extremely healthy and active septuagenarians presenting with a stroke in the setting of a provoked DVT (e.g., traveling back from a ski vacation) would seem to have a PFO-related stroke despite a low RoPE score.

The attempts to quantify the likelihood that a PFO is the culprit pathway for a cryptogenic stroke were performed prior to the results of the recently published randomized trials (long-term RESPECT, REDUCE, CLOSE, and DEFENSE-PFO), which demonstrated that percutaneous PFO closure significantly reduced the risk of recurrent stroke compared with standard of care medical therapy (Chapters 6 and 7) [5,6,8]. These studies proved that a PFO could be causally related, and with appropriate patient selection, the risk of recurrent stroke could be reduced

or prevented. The argument that a PFO is just an innocent bystander in most patients is no longer tenable. Moreover, PFO closure was at least equivalent to medical treatment in all comparative studies. This should have established PFO closure as an alternative treatment to anticoagulation in these patients prior to the significantly positive randomized trials becoming available, especially with the recognition that anticoagulation continues to cause bleeding over years of therapy.

A RoPE Score calculator is available for free online at MDCalc (https://www.mdcalc.com/risk-paradoxical-embolism-rope-score).

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