Patient Selection for PFO Closure Based on the RoPE Study

Can a CHADS-like risk score help to predict who will benefit from PFO-specific therapy in the cryptogenic stroke population?

BY DAVID E. THALER, MD, PHD, FAHA

The possibility that a foramen ovale can be patent into adulthood has been known since it was described by Leonardo Botali in the 16th century. In 1877, Connheim described paradoxical embolism.[1] The paradox, of course, is the appearance of a venous-source thrombus in the arterial circulation that requires bypassing the pulmonary filter through a right-to-left shunt. The discovery of a thrombus trapped in a patent foramen ovale (PFO), either on in vivo imaging such as echocardiography or postmortem via autopsy, is the most compelling evidence for this phenomenon. However, this is such a rare occurrence that presentations at international conferences on the topic routinely recycle the same handful of published images—belying the infrequency of individual discovery by most of us.

Why is it that we believe that a PFO is causally related to some strokes even without discovering a culprit thrombus trapped in the defect? The most compelling observation is an epidemiologic one. The prevalence of PFOs in the general population is approximately 25%. However, in cryptogenic stroke (CS) populations (ie, patients with stroke of unknown etiology despite extensive testing), PFOs are clearly overrepresented, with a prevalence of approximately 50%.[2] If 30% of the 800,000 strokes that occur in the United States each year are cryptogenic, and if half of these patients are found to have a PFO, the combination of CS and PFO occurs in 120,000 patients each year.[3] The most commonly invoked mechanism of PFO-related stroke is paradoxical embolism. However, in situ thrombus formation and an increased susceptibility to embologenic arrhythmias have also been suggested.[4] The epidemiologic data have not addressed the relative frequencies of these mechanisms.

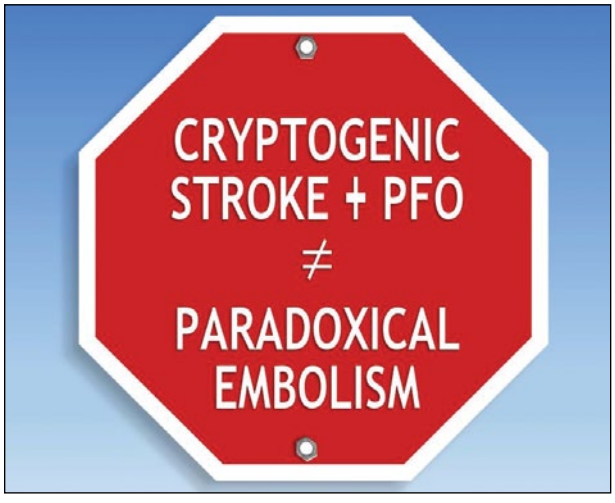

Figure 1. Discovery of a PFO in an individual patient with an otherwise occult etiology is not synonymous with diagnosing paradoxical embolism.

Even accepting that PFOs are causally related to some strokes, the discovery of a PFO in an individual patient with an otherwise occult etiology is not synonymous with a diagnosis of paradoxical embolism (Figure 1). Other stroke mechanisms may be present in patients with CS even if they have a PFO. These mechanisms include lacunar disease,[5] undetected atrial fibrillation (how long was the patient monitored in order to exclude it?), hypercoagulable states, and aortic atheroma and

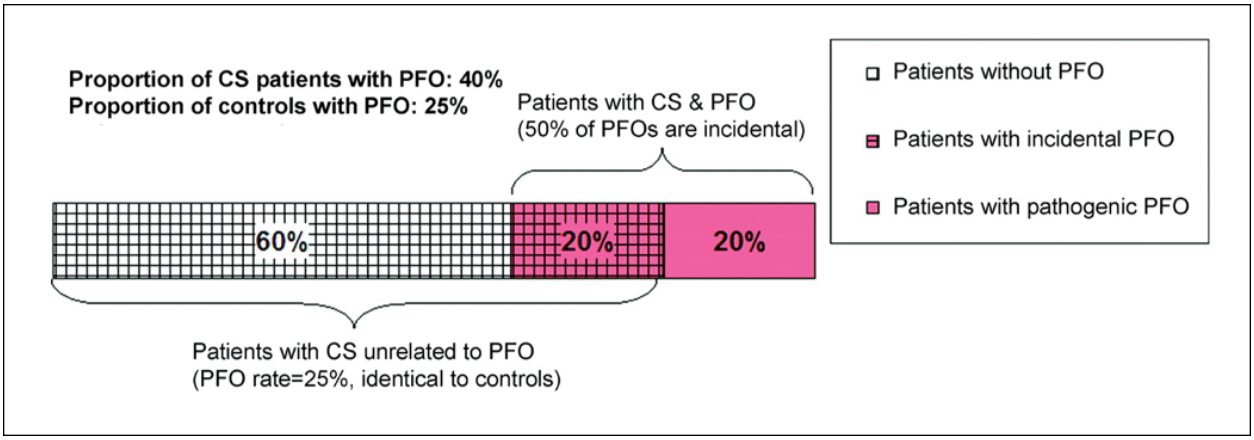

Figure 2. The proportion of patients with CS and PFO with incidental PFO. This figure shows how the proportion of incidental versus pathogenic PFO in patients with CS can be calculated on the basis of the prevalence of PFO in CS patients and in controls. As indicated, when the prevalence of PFO in the CS population is 40% and the prevalence of PFO in the control group is 25%, then 50% of PFOs discovered in CS patients would be incidental. This is based on the assumption that CS patients who have strokes from causes unrelated to PFO will have the same PFO prevalence as the control group (in this case, 25%). Adapted with permission from Alsheikh-Ali AA, Thaler DE, Kent DM. Patent foramen ovale in cryptogenic stroke. Incidental or pathogenic? *Stroke.* 2009;40:2349–2355.

embolism.[6] It is possible that PFO closure devices could even be contraindicated in some of these patients. There may be an exacerbation of atrial fibrillation episodes[7] or an increased chance of thrombus forming on a device in those with hypercoagulable states. For any treatment, the benefit (here, reduced stroke) must outweigh the risks (hemorrhage, procedural, and late device complications) in a medically meaningful way. Treatment options for secondary stroke prevention include those that are less specific for PFO, such as risk factor modification and antithrombotic drugs, and those that are more specific for PFO, such as endovascular or surgical closure. Closing incidental PFOs is not likely to confer much benefit and exposes patients to procedural and device risks. Recent randomized trials of PFO closure versus medical therapy[7-9] that missed their primary endpoints (some by only a stroke or two in the "wrong" group) indicate a need for careful patient selection. Appropriate patients for PFO-specific therapy are those with a high "PFO-attributable recurrence risk," which is a function of the probability that a PFO is pathogenic (in a CS patient) and the risk of recurrent CS.

WHEN IS A PFO LIKELY TO BE PATHOGENIC?

The excess prevalence of PFO in the CS population is strong evidence for a causal relationship. However, within the CS population, the patients with strokes unrelated to PFO (ie, those without PFOs altogether and those with incidental PFOs) must have a PFO prevalence that matches the general population from which they come. Of course, there is nothing about having a PFO-unrelated CS stroke that should reduce the likelihood of PFO. Therefore, given certain assumptions (Figure 2), roughly half of the PFOs discovered in patients with CS will be incidental.[10] Is it possible to disaggregate discovered PFOs into PFOs that are more or less likely to have been culprits? Another way to ask this is, "Are there patient-level variables that predict the discovery of a PFO from within a CS population?"

The Risk of Paradoxical Embolism (RoPE) study was designed to address this question.[11] Investigators combined 12 existing cohort studies from the published literature (and some unpublished data) to create the largest patient-level database of those with CS and known PFO status.[2] All subjects had undergone either transesophageal echocardiography or transcranial Doppler screening. Some patients had PFOs, and some did not. Using clinical and radiological data available at the time of the index stroke, variables were identified that were associated with having or with not having a PFO. A multivariate regression model identified six variables that were associated with PFO status, creating a simple 11-point score (0–10) (Table 1).[12]

High RoPE scores identify younger patients without conventional vascular risk factors and with infarcts located superficially in the brain (more likely embolic); low RoPE scores identify older patients with deep infarcts and multiple conventional risk factors. The RoPE score successfully disaggregates CS patients into a stratum with a PFO prevalence that matches the background population (23%, RoPE scores 0–3), which then increases in a

TABLE 1. RoPE SCORE CALCULATOR		
Characteristic	**Points**	**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 (y)		
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 y without vascular risk factors, no history of stroke or TIA, and cortical infarct)		10
Minimum score (a patient ≥ 70 y with vascular risk factors, prior stroke, and no cortical infarct)		0

linear fashion to the highest RoPE scores with a very high prevalence of PFO (73%, RoPE scores 9–10). Applying Bayes' theorem, and with the assumption that the background prevalence of PFO is 25%, one can estimate the PFO-attributable fraction (ie, the probability that the index event was related to the PFO) for each RoPE score stratum, yielding a satisfying and clinically meaningful range of 0% to 88%.

An important observation from the RoPE database was that patients in different strata had very different 2-year stroke and transient ischemic attack (TIA) recurrence rates. Those most likely to have had PFO-related index events (high RoPE scores) had a lower risk of recurrence than those with the lower RoPE scores, suggesting that the natural history of PFO-related events is more benign than the other non–PFO-related (but still occult) CS mechanisms, but is more aggressive (with respect to repeat events) than PFO-related stroke. This finding is also instructive with regard to interpreting older observational studies that did not have the benefit of RoPE score stratification. The natural history of CS and PFO, upon which clinical trial assumptions of recurrence were based, would have included patients with a wide range of RoPE scores and so would have overestimated the recurrence risk of PFO-related events.[13] Those with non–PFO-related index events would not be likely to have a beneficial treatment effect from PFO closure, and so the "negative" results of the PFO closure trials may be more a function of including patients in the cohorts who were never likely to show a benefit rather than a failure of the treatment per se, if only it had been studied in the right population.

ARE THERE BASELINE VARIABLES THAT PREDICT RECURRENT STROKE, AND DO THOSE PREDICTORS DIFFER BY ROPE SCORE?

Predictors of PFO-related stroke recurrence have not been firmly established, but authors and expert groups have offered them nonetheless.[14,15] The first error in this regard has been the conflation of two different risk dimensions, namely, (1) the confidence in the PFO-related diagnosis of the index event, and (2) predictors of recurrence. So, for example, it has been suggested that patients who experienced an antecedent period of prolonged immobility (eg, an airplane flight) and who were performing a Valsalva maneuver at the onset of symptoms (eg, collecting luggage) were the ones with "clinically significant" PFOs. It is hard to argue with the compelling circumstantial evidence that such an event would be PFO related. However, this is not the same as identifying a PFO at high risk for recurrence and a patient likely to benefit from PFO-specific therapy. In fact, it is equally plausible that such a patient might be at a lower risk of recurrence. In such a scenario, the PFO needed to be prodded into pathogenicity by an unusually high burden of venous thromboemboli and an increase in right-to-left shunting with the Valsalva maneuver. Might not such a PFO be seen as more resistant to allowing a paradoxical embolism and thus less likely to permit recurrence than a PFO that was associated with stroke even when it was not so provoked? It is important to keep these two risk dimensions separate.

In the article by Wu, there was a table titled "Clinical and Morphologic Features Associated With Recurrent Paradoxical Embolic Events." In it, there were two categories of such features: clinical ones such as Valsalva at onset, and echocardiographic ones such as shunt size. To support the claims in the table that those features predicted recurrence, 11 references are cited. However, of those 11 references, six were without recurrence data entirely, another four were not studies of patients with CS, and one was a CS population but with no recurrent events! The entire table was predicated on data that could not be informative.

Mas et al were the first to show a statistical association with recurrent stroke in CS patients if their PFO was also

associated with an "atrial septal aneurysm" (a somewhat confusing term that refers to hypermobility of the interatrial septum).[16] Others have not confirmed that finding.[17] Other anatomic and physiologic characteristics of PFOs, such as prominent Eustachian valves, Chiari networks, size of shunt, and shunting at rest (without requiring Valsalva), have shown inconsistent findings with regard to recurrence.[18]

The RoPE database offers a better opportunity to assess risk predictors and to discern whether those predictors differ based on RoPE scores. Although the component studies that made up the database each had different variables and definitions, the dataset was harmonized to include three echocardiographic features purported to indicate high risk: shunting at rest, shunt size (as measured by bubble counts), and a hypermobile interatrial septum. The data show that patients with CS and PFO are not homogenous and that baseline variables associated with recurrence differ by RoPE strata. Analyses were performed with patients dichotomized into a group with high RoPE scores (> 6) and a group with low RoPE scores (≤ 6). None of the echocardiographic variables were associated with recurrence in the low RoPE score group—as would be expected because those PFOs were most likely incidental, and the strokes were due to other mechanisms. However, in the high RoPE score group, two of the three PFO characteristics were influential.

As shown by the original PFO/ASA study in 2001, a floppy septum together with a PFO increased the risk for recurrence significantly, with an adjusted hazard ratio of 2.31 (95% confidence interval, 1.05–5.05).[16] Surprisingly, shunt size was also related to recurrence but in a direction contrary to what was predicted (ie, patients with small shunts were 3.26 [95% confidence interval, 1.59–6.67) times more likely to have a recurrent stroke or TIA than those with large shunts).[19]

DISCUSSION

There are three potential explanations for the surprising small-shunt finding: (1) it is wrong and a type I error based on statistical chance; (2) there were biases in the dataset that led to the finding, and large shunts nevertheless are riskier (eg, more patients with large shunts were closed during the follow-up period and removed from the analysis, an example of informative censoring); and (3) it is right and challenges our current assumptions about PFO-related stroke. A frequently heard, but untenable, criticism is that the variable is simply unreliable—arguing that bubble counts may change from moment to moment, interobserver reliability is low, and transesophageal echocardiography protocols are not standardized. All true. However, if the data were just random noise, then they should have been noninformative, and the association should have reverted to the null. That is not the case. There is a powerful effect but in an unpredicted direction. With regard to the informative censoring, sensitivity analyses done with the RoPE dataset (eg, assigning closed subjects double or even triple the observed stroke/TIA rate) did not remove the much higher risk of recurrence with small shunts. The powerful effect persisted.

There is another explanation that is consistent with the data and should lead to testable hypotheses. It may be that there is more than one PFO-related stroke mechanism. Paradoxical embolism is clearly one of them, but perhaps it is a less risky mechanism than a PFO-related stroke mechanism associated with a small shunt. It is possible that patients with small shunts have PFOs that are more often closed with small amounts of stagnant blood within the tunnel prone to forming thrombus in situ. It only takes a thrombus of 3 mm or so to occlude a middle cerebral artery. A 1- or 2-mm thrombus could easily cause symptoms if it embolized into the cerebral or retinal circulations. Although unconventional, it is biologically plausible and concordant with the findings from RoPE. However, this possibility leads to potentially different treatment decisions with regard to closure. A CS patient with a high RoPE score and a small shunt should perhaps not be reassured that his or her PFO is "just a small one," with the implication that it confers lower risk because of it.

The goal of RoPE is ultimately to identify a group of patients who are more likely to benefit from PFO-specific therapy, such as endovascular closure, so that therapy and resources can be appropriately targeted and to avoid unnecessary interventions. This is similar to the CHA2DS2-VASc[20] and HAS-BLED[21] scores for determining antithrombotic treatment in patients with atrial fibrillation. There are many examples of when a beneficial treatment effect is dependent on identifying those with a high risk of the outcome of interest (eg, symptomatic carotid stenosis of > 70% [or perhaps 50%] and carotid revascularization[22] or high CHADS2 scores in atrial fibrillation and anticoagulation).[22] Cryptogenic stroke and PFO is no different except given the frequency of their co-occurrence, the need for careful patient selection may be even more pressing than in other conditions. The RoPE score can help to provide a probability that an individual patient's stroke was PFO related. Predictors of recurrence differ by RoPE strata. Note that variables that predict one risk dimension may be noninfluential for the other. Younger age and the absence of vascular risk factors predict PFO but have no bearing on recurrence in the high RoPE score group. Once these two risk dimensions are combined, we may have a method of identifying patients with a high PFO-

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attributable recurrence risk who may derive particular benefit from PFO-specific therapy, such as endovascular closure. Such a combined model will be validated on the combined clinical trial populations from RESPECT, the PC-Trial, and CLOSURE-I.[11] If the models work, PFO closure can be offered to a targeted population that is based on methodologically solid evidence rather than clinical hunches. ■

David E. Thaler, MD, PhD, FAHA, is Interim Chairman, Department of Neurology, Tufts University School of Medicine in Boston, Massachusetts. He has disclosed that he is on the Steering Committee for the RESPECT trial (St. Jude Medical) and receives NINDS funding. Dr. Thaler may be reached at dthaler@tuftsmedicalcenter.org.

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