Recurrent stroke on imaging and presumed paradoxical embolism

A cross-sectional analysis

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ABSTRACT

Objective: To identify whether factors supporting a diagnosis of paradoxical embolism (i.e., venous thrombosis or Valsalva maneuver) are associated with radiologic markers of recurrent strokes in patients with patent foramen ovale (PFO) and cryptogenic stroke (CS). Such clinical indicators of paradoxical embolism are commonly viewed as risk factors for CS recurrence, but precise risk estimates are lacking.

Methods: Data from the prospective Tufts PFO Registry collected at the time of the index CS were analyzed. We defined the following radiologic markers of stroke recurrence: 1) strokes of different radiologic ages and 2) silent strokes (detected on MRI but without symptoms preceding the index event). We examined the association between the radiologic endpoints and the clinical indicators of paradoxical embolism with multivariate logistic regression models, adjusting for age and gender.

Results: Data were available for 224 subjects. Strokes of different radiologic ages were not associated with the thrombosis-predisposing conditions (1.2 [95% confidence interval 0.5–2.7]), the Valsalva maneuver (1.3 [0.6–3.1]), or the presence of either of these factors. No statistically significant association was found in subgroups stratified by anatomic location of the index stroke or for the outcome of silent strokes.

Conclusions: Our negative findings do not lend support to using the presence of clinical indicators of paradoxical embolism as an indication for percutaneous PFO closure. Factors that support a paradoxical embolism mechanism may be different from those that predict paradoxical embolism recurrence. Further investigations with clinical follow-up and larger sample sizes are needed to reach more precise estimates for the associations examined. *Neurology*® 2012;78:993–997

GLOSSARY

CI = confidence interval; **CS** = cryptogenic stroke; **FLAIR** = fluid-attenuated inversion recovery; **OR** = odds ratio; **PFO** = patent foramen ovale; **TOAST** = Trial of Org 10172 in Acute Stroke Treatment.

Cryptogenic strokes (CSs) are those for which extensive clinical and laboratory workup failed to identify a definitive cause. A patent foramen ovale (PFO) is frequently found in patients with CS, and, thus, the stroke mechanism is commonly attributed to paradoxical embolism.^{1,2} Although several case reports of patients with impending paradoxical embolism clearly demonstrate that PFO can be the conduit for right-to-left crossing of thrombi,³ the paradoxical embolism diagnosis in patients with CS and PFO is a presumptive one.^{4,5} Approximately one-third of discovered PFO in patients with CS is likely to be unrelated,^{4,5} and even among PFO-attributable strokes, the mechanism of stroke may be embolic but not paradoxical, such as in situ thrombogenesis or arrhythmogenesis.^{6,7}

Because of the uncertainty involved in reaching the paradoxical embolism diagnosis, clinicians often seek factors mechanistically related to the paradoxical embolism phenomenon to support its diagnosis.⁸ Thus, the presence of a venous thrombus (or thrombogenesis-

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predisposing conditions, such as prolonged immobility) and circumstances that intensify the right-to-left shunt (increase in right atrial pressure through a Valsalva maneuver) are thought to be supportive of a paradoxical embolism diagnosis.⁸ However, the implications of these provoking paradoxical embolism factors are unclear with regard to prediction of the risk of future CS and therapeutic decision making.

We aimed to identify whether clinical indicators of paradoxical embolism are associated with radiologic markers of recurrence in a cross-sectional study using data from a registry of patients with CS and PFO.

METHODS Subjects. We analyzed data of patients included in the Tufts PFO Registry up to August 2011. This is a prospective registry of patients with CS (or TIA) and PFOs, established in 1998. This study was approved by the local institutional review board. Data collected at the time of the index CS include demographic information, medical and family history, and radiologic, serologic, and echocardiographic variables. Activity at the onset of symptoms is recorded as is the presence of any prothrombotic condition (see definition below). Cryptogenic ischemia (stroke and TIA) is defined as a sudden-onset neurologic deficit in a vascular territory most likely due to cerebral ischemia and without an identifiable cause despite complete investigations. We adhered to definitions according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification,⁹ except for our definition of small vessel disease, which was stricter. Subjects were excluded from the registry as having non-CS if they had a clinical lacunar syndrome with an infarct in the territory of a single penetrating artery and any one of the following: 1) age >50 years, 2) diabetes, or 3) hypertension. There is little guidance from the TOAST classification as to how to define a hypercoagulable state. For the purposes of the Tufts PFO Registry only, patients with a clear hypercoagulable syndrome, i.e., multiple recurrent deep venous thromboses and arterial thrombi with hypercoagulable testing that are thought to be associated with arterial events rather than venous, were excluded. These tests were considered to be the lupus anticoagulant, the anticardiolipin antibody, hyperhomocysteinemia, and β_2 microglobulin.¹⁰ Subjects with venous hypercoagulable abnormalities (protein C or S deficiency, antithrombin III deficiency, factor V Leiden, and a prothrombin gene mutation) were not excluded. A complete investigation in the Registry was defined as brain imaging (CT or MRI), cerebrovascular imaging (CT angiography, magnetic resonance angiography, catheter angiography, or carotid artery ultrasound), cardiac echocardiography (transesophageal echocardiography preferred), extended cardiac rhythm monitoring, and hypercoagulable testing.

Clinical definitions. We defined 2 types of clinical conditions as supportive factors of the paradoxical embolism diagnosis, which were thoroughly sought in all subjects included in the Tufts PFO Registry: 1) prothrombotic conditions: prolonged immobility (hours) in the 2 weeks before the index event (e.g., prolonged travel), postoperative period, or concurrent diagnosis of deep vein thrombosis; and 2) a Valsalva maneuver immedi-

ately preceding neurologic symptom onset, e.g., lifting weights, vomiting, bowel movement, sexual activity, and coughing. Subjects with at least one of the 2 conditions were defined as having PFO with a provoked paradoxical embolism, i.e., an embolism through the PFO that was provoked by the presence of these clinical conditions.

Radiologic and echocardiographic definitions. Chronic brain infarcts were defined as focal brain lesions hyperintense on T2-weighted images and hypointense on T1-weighted imaging and as having a minimum diameter of 3 mm (maximum linear measurement in any direction). Surrounding fluid-attenuated inversion recovery (FLAIR) hyperintensity was viewed as supportive. Acute and subacute infarcts, usually associated with a clinical history, are expected to be hyperintense on diffusion-weighted imaging and FLAIR ($\pm$ T2) but without the requirement of being hypointense on T1-weighted images. For subjects with only CT scans, acute infarcts are hypodense, but not as dense as CSF, often with mass effect, chronic infarcts are those with density that approximates the CSF with no mass effect and often with adjacent ventricular dilation, and subacute infarcts are intermediate in density between acute and chronic infarcts. Large strokes were defined as those with a maximum linear measurement of 15 mm. With regard to their anatomic location, strokes were classified as cortical if neuroimaging showed that they extended into the cerebral cortex, the periphery of the cerebellar hemispheres, or the cortical border zones between the anterior cerebral artery and the middle cerebral artery or between the posterior cerebral and the middle cerebral artery. Subcortical strokes were defined as those that were restricted to the deep white matter of the cerebral or cerebellar hemispheres, the subcortical gray matter structures, or the internal border zone of the middle cerebral artery.

The following radiologic markers of stroke recurrence were examined: 1) strokes of different radiologic ages: subjects who had any combination of acute, subacute, and chronic strokes on neuroimaging at the time of the index event; and 2) silent strokes: chronic stroke(s) detected on MRI but without symptoms preceding the index event in the subject's history.

From transesophageal echocardiographic studies, we recorded 1) the presence of an atrial septum aneurysm (excursion of the interatrial septum >10 mm from the midline¹¹) and 2) the presence of shunting at rest, i.e., not requiring a Valsalva maneuver, on either the agitated saline contrast or color Doppler flow image.

Statistical analysis. Clinical and radiologic data of included subjects are presented with descriptive statistics. We tested for associations between the provoking paradoxical embolism clinical conditions and the radiologic endpoints of stroke recurrence with logistic regression models, with both unadjusted and adjusted estimates for the confounders of age and gender. Associations are expressed as odds ratios (ORs) with the corresponding 95% confidence intervals (CIs). To examine whether these associations are different for patients with strokes in different vascular territories, we performed subgroup analyses stratified by the anatomic location (cortical vs subcortical) of the index stroke at the time of entry in the Tufts PFO Registry. Furthermore, we explored whether the associations between the provoking paradoxical embolism conditions and the radiologic markers of recurrence are modified by the echocardiographic characteristics of the PFO (presence of atrial septal aneurysm or shunt at rest). Thus, we included interaction terms between the clinical conditions of interest (prothrombotic conditions, Valsalva maneuver, or both) and the echocardiographic characteristics in logistic re-

Table 1 Descriptive characteristics of subjects included in the Tufts PFO Registry

Baseline variables in the Tufts PFO Registry (n = 224)	
Men, n (%)	127 (57)
Age, y, mean (SD)	52.3 (14.3)
Clinical conditions for provoked paradoxical embolism, n (%)	
Prothrombotic conditions	83 (37)
Concurrent deep vein thrombosis	13 (6)
Prolonged immobility or postoperative period	73 (33)
Valsalva maneuver	60 (27)
Either prothrombotic conditions or Valsalva maneuver	121 (54)
Both prothrombotic conditions and Valsalva maneuver	22 (10)
Transesophageal echocardiographic data (n = 176), n (%)	
Atrial septal aneurysm	41 (23)
Positive agitated saline study at rest	135 (77)
Positive agitated saline study with Valsalva maneuver only (negative study at rest, n = 41)	30 (73)
Radiologic brain imaging data (n = 189)	
Strokes of different radiologic ages	43 (23)
Index cortical stroke	124 (66)
Index subcortical stroke	49 (26)
Index strokes in multiple vascular territories	16 (8)
Silent strokes	38 (17)
Large acute stroke	83 (51)
Largest acute stroke diameter, mm, mean (SD)	27.1 (22.0)

Abbreviation: PFO = patent foramen ovale.

gression models and checked for statistical significance ($p < 0.05$) of the interaction terms.

As a secondary analysis, we also explored whether provoking paradoxical embolism conditions are associated with large acute strokes. We examined these associations with logistic regression models in which the large acute strokes were defined as dichotomous variables (≥ 15 mm) and with linear regression models in which the size of the largest acute stroke in each patient was analyzed as a continuous variable.

RESULTS The Tufts PFO Registry included data for 224 subjects. Descriptive characteristics are shown in table 1. The mean age of patients was 52.3 years, and 57% were men. A small proportion of patients tested positive in hypercoagulable testing (6.6% were heterozygous for factor V Leiden and 3.6% for the 20210A prothrombin gene mutation). Prothrombotic conditions (i.e., prolonged immobility, postoperative period, or concurrent diagnosis of deep vein thrombosis) were present in 37% of the subjects. Valsalva maneuver at the time of stroke

symptom onset was reported by 27%. About one-half of the patient population had one of these 2 conditions present (provoked paradoxical embolism), but the concurrent presence of both conditions was found only in 10% of the subjects. Radiologic data were available for 189 subjects; 92% of patients had MRI data available, and 8% had data from CT imaging. Missing radiologic data were considered as being missing completely at random, because no known factor potentially associated with missingness could be identified. Testing for differences in the distribution of age or gender between subjects with and without available radiologic data did not show any statistically significant differences. Strokes of different radiologic ages were found in 23% of patients; the majority of these strokes were clinically silent, because 17% of subjects had findings of a chronic stroke on MRI without a prior history of ischemic neurologic symptoms. Approximately one-half of the index strokes (51%) were measured as large. Of index strokes, 66% were mapped as cortical, 26% were subcortical, and 8% were strokes in multiple vascular territories. The transesophageal echocardiographic data showed that 23% of patients had atrial septal aneurysms, whereas the agitated saline study showed positive results at rest in 77% of the patients.

The results of testing for associations between strokes of different radiologic ages and the clinical conditions of interest are shown in table 2. Neither prothrombotic conditions nor the Valsalva maneuver was associated with the radiologic endpoint of strokes of different ages (adjusted OR [95% CI] = 1.19 [0.54–2.67] and 1.30 [0.58–3.09], respectively). Similarly, no significant association was found between the presence of either or both of the provoking paradoxical embolism conditions with strokes of different ages. No significant association was found for the radiologic endpoint of silent strokes either. The results were essentially unchanged in unadjusted analyses. Similarly, no significant associations were found in the subgroups of patients with cortical or subcortical index strokes. By examining the interactions between transesophageal echocardiographic parameters (atrial septal aneurysm or positive agitated saline study at rest) with the provoking paradoxical embolism conditions, we did not find any evidence of effect modification on the association with the radiologic endpoints (all interaction $p > 0.05$).

In the secondary analysis for the outcome of large acute strokes, no significant association of the clinical conditions (in any combination) was found with the dichotomous outcome of large acute stroke or the size of the largest acute infarct ($p > 0.05$).

Table 2 Associations between radiologic endpoints of interest and clinical indicators of paradoxical embolism^a

Clinical conditions	Strokes of different radiologic ages	Silent strokes	Large acute strokes
All patients			
1: Valsalva maneuver	1.30 (0.55–3.09) [1.23 (0.58–2.60)]	1.03 (0.45–2.32) [0.97 (0.44–2.14)]	0.67 (0.31–1.47) [0.74 (0.36–1.52)]
2: Prothrombotic conditions	1.19 (0.54–2.67) [1.01 (0.49–2.04)]	0.61 (0.27–1.33) [0.65 (0.30–1.38)]	1.44 (0.73–2.86) [1.41 (0.73–2.68)]
1 or 2	1.29 (0.59–2.79) [1.37 (0.68–2.73)]	0.78 (0.38–1.59) [0.82 (0.41–1.65)]	1.01 (0.52–1.95) [1.04 (0.56–1.93)]
1 and 2	1.25 (0.30–5.14) [0.66 (0.18–2.37)]	0.52 (0.11–2.40) [0.46 (0.10–2.06)]	1.12 (0.32–3.93) [1.18 (0.34–4.04)]
Patients with index cortical stroke			
1: Valsalva maneuver	1.68 (0.61–4.62)	1.49 (0.55–4.03)	0.83 (0.32–2.12)
2: Prothrombotic conditions	1.16 (0.50–2.74)	0.99 (0.41–2.39)	2.17 (0.93–5.06)
1 or 2	1.84 (0.74–4.59)	1.34 (0.56–3.22)	1.57 (0.71–3.42)
1 and 2	1.04 (0.19–5.64)	0.95 (0.18–4.96)	1.78 (0.29–10.8)
Patients with index subcortical stroke			
1: Valsalva maneuver	0.40 (0.05–2.97)	0.28 (0.04–2.04)	1.30 (0.26–6.51)
2: Prothrombotic conditions	0.62 (0.10–3.59)	NA	0.76 (0.15–3.79)
1 or 2	0.49 (0.10–2.40)	0.09 (0.01–0.62)	0.62 (0.14–2.71)
1 and 2	0.27 (0.01–7.68)	NA	2.16 (0.24–19.4)

Abbreviation: NA = not applicable.

^a Data are odds ratio (95% confidence interval), adjusted for age and gender [unadjusted].

DISCUSSION In a cross-sectional analysis of patients from the Tufts PFO Registry, we found no significant associations between the clinical conditions that support a paradoxical embolism diagnosis and radiologic markers of stroke recurrence. The lack of association between the clinical factors and the radiologic endpoints persisted in subgroups of patients with cortical vs subcortical index strokes, and there was no evidence that there is a differential association in patients with atrial septal aneurysms or spontaneous shunting at rest. Similarly, no association was found between large strokes and provoked paradoxical embolism.

Consequently, our negative findings do not lend support to using the presence of clinical indicators of paradoxical embolism as an indication for percutaneous PFO closure.^{12–14} Although it is intuitively attractive that a confident diagnosis of paradoxical embolism (young patient, prolonged immobility, and Valsalva maneuver at symptom onset) would predict a high-risk patient, factors that support a paradoxical embolism mechanism for an index CS may be different from those that predict paradoxical embolism recurrence. Perhaps a high-risk PFO is one that is not provoked (i.e., not subjected to a high burden of thromboembolism and not requiring a Valsalva maneuver to change the hemodynamics in favor of shunting) but one that produced a paradoxical

cal embolism anyway. Until the emergence of more conclusive data, our findings suggest that such clinical conditions cannot be viewed as decisive determinants of therapeutic options for PFO.

Our observational study has limitations that warrant cautious interpretation of our results. By design, our study did not involve prospective follow-up of CS patients for recurrent events; radiologic markers were used as surrogates for recurrence instead. Although clinical data were collected at the time of the index event, the association examined here was with events occurring in the past. Despite this asymmetry, the inference we aimed to draw was whether patients with the clinical profile of provoked paradoxical embolism have a malignant clinical course with regard to recurrent strokes. To this end, we used brain imaging as an indisputable recording of recurrent stroke in the patients' past. This also has the advantage of increasing the number of observed outcomes (23% in this study). We acknowledge that the retrospective nature of these observations is vulnerable to survival bias; i.e., if patients with provoked paradoxical embolism experience severe and potentially fatal strokes, then any association with recurrence would be attenuated. However, we observed that the conditions provoking paradoxical embolism were not associated with large strokes in our dataset, and prior studies indicate that the clinical course of CS-PFO cohorts is not characterized by large mortality rates.^{15–17} Thus, survival bias is an unlikely explanation for our negative findings.

Despite the rarity of recurrent clinical events in the CS and PFO population, prospective studies with radiologic follow-up can further inform the clinical question raised by our study.¹⁸ Furthermore, the etiology of the prior strokes in our patient population is theoretically unknown, because the CS diagnosis was reached for the index stroke. However, given that most of the prior strokes in our database were clinically silent and the majority of the non-CS etiologies are not transient in nature (e.g., carotid artery disease or heart valvular abnormalities), we can safely deduce that the etiology of prior strokes was probably cryptogenic in the majority of our patient population.

Another limitation of our study is the modest sample size. As illustrated in table 2, the CIs for certain associations were wide, and our study cannot exclude a significant role for the clinical conditions provoking paradoxical embolism. However, all OR point estimates were very close to 1, indicating that despite the imprecision in estimates imposed by the available sample size, the plausible effect sizes of these factors are small to modest. Although we did not identify any significant interactions between the clinical conditions of interest and echocardiographic variables

of the PFO, the statistical power of our interaction testing is limited by the available sample size.

Our study shows that the conditions that are commonly viewed as supportive of a diagnosis of paradoxical embolism are not associated with radiologic markers of stroke recurrence. Our negative findings require validation from prospective investigations with clinical and radiologic follow-up and larger sample sizes. The range of effect sizes observed in our study will be helpful in designing and planning future observational studies that aim to address the risk conferred by clinical indicators of paradoxical embolism.

AUTHOR CONTRIBUTIONS

Dr. Kitsios: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision. A. Lasker: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, statistical analysis. Dr. Singh: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Dr. Thaler: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision, obtaining funding.

DISCLOSURE

Dr. Kitsios serves on the editorial board of the *World Journal of Methodology*. A. Lasker and Dr. Singh report no disclosures. Dr. Thaler serves on a data safety monitoring board for Lantheus Medical Imaging and as a consultant for AGA Medical Corporation and WL Gore Associates.

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