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Review Article

Patent foramen ovale and stroke: More closure to closure but concerns remain-a review

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ABSTRACT

A patent foramen ovale (PFO) is a persistent opening between the right and the left atrium that fails to close spontaneously after birth. An estimated 25% of all adults harbor this condition making it the commonest congenital cardiac anomaly in the general population. Presence of a PFO has long been implicated in causing strokes in the young even though it does not produce any cardiopulmonary hemodynamic perturbations. Patient management has traditionally relied on prophylaxis with antiplatelet medications or occasionally anticoagulants. Good quality evidence supporting surgical or mechanical closure of PFOs following a stroke had been lacking. Publication of 3 new randomized controlled trials in a recent edition of the New England Journal of Medicine is expected to reinforce calls for closing PFOs with percutaneous closure devices in stroke patients. While these trials provide answers to important questions in stroke prevention, it also raises concerns about injudicious extrapolation of these results and indiscriminate use of these devices in practice. The aim of this article is to review the background, pathophysiology and current level of evidence for secondary stroke prevention from PFO and highlight some pitfalls in management.

Contents

1. Background

The first written documentation of an association between a patent foramen ovale (PFO) and a stroke dates back to 1877, when a German pathologist, Cohnheim, described a young woman with an ischemic stroke at autopsy, who had coexisting PFO and deep

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venous thrombosis (DVT).[1] He hypothesized that the thrombus from her leg travelled to the right atrium and crossed over to the left through the PFO before ending its journey in the cerebral artery.[1] Similar descriptions of paradoxical embolism from autopsy studies emerged in the ensuing years. However, it was only in the 1980s with the advent of echocardiography that the diagnosis of PFO in vivo became routine in clinical practice.

PFO is widely prevalent in the population. Data from echocardiography studies show a prevalence of 15–25% in the adult population whereas the detection is slightly higher on autopsy studies ranging between 15 and 35%.[2–6] In terms of a perspective, these figures reflect a prevalence that is 10-fold higher than that of bicuspid aortic valve, which is considered to be the most common adult congenital heart disease.[7] Some observational studies have implied that the frequency of PFO decreases with increasing age suggesting that spontaneous closure can occur in later years of life.[2,3,6] However, longitudinal studies on PFOs to either support or refute this claim are currently lacking. Both men and women are affected equally and there are no clear cut race-ethnic predilections.[2,6]

2. Pathophysiology of stroke from a PFO

There is considerable variability in size and morphology of PFOs, which can have notable influence on the risk of stroke. Large sized PFO have been associated with a higher stroke risk in observational studies.[8,9] Presumably, a larger aperture can facilitate paradoxical embolism especially during Valsalva type maneuvers, which increases right atrial and ventricular pressures, easing the migration of the thrombus from the right to the left side of the heart. However, a thrombus in transit has only been identified in a handful of cases. PFOs are also associated with other structural anomalies, such as atrial septal aneurysm (ASA), prominent Chiari network and Eustachian valves. Atrial septal aneurysm refers to hypermobility of the inter-atrial septum from its midline position during the cardiac cycle; traditionally an excursion of $\geq$10 mm is considered diagnostic for an ASA. Presence of these associated features can increase the risk of paradoxical embolism by preferentially directing flow from the inferior venacava to the foramen ovale. In addition, ASA may lead to insitu thrombus formation, atriopathy or provoke atrial fibrillation.[10] Inherited or acquired prothrombotic states increases the risk of cerebral embolism in patients with PFO. Studies show an increased prevalence of protein C and S, antithrombin III deficiencies, as well as Factor V Leiden and prothrombin gene mutation in stroke patients with a PFO.[11–13] Similarly, recent surgery, trauma, dehydration or use of oral contraceptives can also elevate stroke risks in these patients. The most proximate mechanism operative in an individual patient may on occasions be difficult to identify and it is possible that more than one mechanism is responsible.

3. Epidemiology

Epidemiological investigations of the relationship between ischemic strokes and PFO can be challenging due to the high prevalence of this risk factor in the general population. Statistical association can be erroneous if they are not carefully controlled for conventional stroke risk factors. This is especially true for the elderly population who often harbor other competing conditions that independently increase their stroke risk. Presence of a PFO will likely be incidental in this situation. The cause of stroke remains unknown in about a third of patients with an ischemic stroke despite a detailed work-up.[14] This group of so called *cryptogenic* stroke patients have a much higher prevalence of a PFO than the general population and strokes in this sub-population shows a significant association with the presence of a PFO, as association that is stronger for the younger age group.[14,15] Conversely, a large meta-analysis of 23 case controlled studies shows that even in a third of patients with cryptogenic infarcts, presence of a PFO is likely incidental, adding to the challenge of clinical care in these patients.[16]

3.1. PFO-incidental or causative?

The discovery of a PFO in a stroke patient raises the question whether the PFO is causative or incidental. Due to the uncertain association between it and a stroke, strokes attributable to a PFO are considered "cryptogenic" though the operative definition of this term has been applied variably in practice. Based on the results of the existing observational studies, a PFO should be considered as a probable cause in younger patients with cryptogenic strokes who have undergone a detailed investigation for their stroke which includes, imaging of intracranial and extracranial vasculature, cardiac monitoring to rule out paroxysmal or persistent atrial fibrillation, a technically good quality echocardiography to look for structural causes for cardioembolism, assessment of other vascular risk factors including hypertension, diabetes, hyperlipidemia, smoking status and in select cases, investigations for underlying prothrombotic states. Magnetic Resonance Imaging (MRI) can further assist in determining the etiology of stroke. Most strokes due to a PFO carry an embolic "signature" on clinical presentation and imaging and disproportionately affect the younger patients who lack established risk factors for stroke. Radiological evaluation of a large database of strokes in patients with a PFO demonstrates that infarcts attributable to PFO are usually larger ($>$10 mm), superficially located, than smaller, or deep strokes, and those associated by chronic infarcts; strokes due to PFO are more often solitary lesions and less likely accompanied with coincidental chronic infarcts on imaging.[17] However, these findings are not absolute and should be considered together with the overall clinical picture in making this determination.

Efforts have been made to develop evidence based clinical tools to aid determining the PFO-relatedness of a stroke in cryptogenic stroke patients. A detailed analysis of a large database with cryptogenic stroke patients, who underwent a systematic, detailed evaluation shows that the attributable risk from a PFO decreases with increasing age, presence of hypertension, diabetes, smoking, prior history of a stroke or a TIA and presence of deep infarcts.[18] A risk stratification system, called the Risk of Paradoxical Embolism (RoPE) score has been developed to stratify patients by the related probability that a discovered PFO is incidental or stroke-related (Table 1).[18] Clinical scales such as this have been useful to address similar problems in statistical analysis and inferences caused by

Table 1
Risk of Paradoxical Embolism (RoPE) score calculator.

Characteristic	Points
No history of hypertension	1
No history of diabetes	1
No history of stroke or a TIA	1
Non-smoker	1
Cortical infarct on imaging	1
Age	
18–29	5
30–39	4
40–49	3
50–59	2
60–69	1
$\geq$ 70	0

Maximum score = 10 (A patient $<$30 years with no history or hypertension, diabetes, prior stroke or TIA, non-smoker with a cortical infarct on imaging).
Minimum score = 0 (A patient $>$70 years with a history of hypertension, diabetes, prior stroke or a TIA, smoking and no cortical infarct).