Stroke

Patent Foramen Ovale, Aneurysm, and Embolic Stroke: Examining the Relationships

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Patent Foramen Ovale: Innocent or Guilty? Evidence from a Prospective Population-Based Study

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Despite the large number of echocardiographic studies suggesting an association between patent foramen ovale (PFO) and atrial septal aneurysm (ASA) and embolic stroke, there remains significant controversy concerning the strength or significance of this relationship. In this study, Meissner and associates seek to prospectively determine the association between PFO and ASA and stroke in a randomly selected population sample participating in the Stroke Prevention: Assessment of Risk in a Community (SPARC) study. The study was prompted by recognized methodologic weaknesses in early published data, including the retrospective nature of analyses, poor selection of controls, and failure to adjust data for age and comorbidities. They point out that the variability and reported stroke risk for PFO ranges from less than 1% to as high as 17.5%, which illustrates the magnitude of this controversy.

To prospectively examine the relationship of PFO and ASA to stroke, an age- and gender-stratified random sample of the Olmsted County, Minnesota, population (45 years or older) consisting of 1475 residents was chosen, of whom 230 were ineligible because of pre-specified exclusion criteria and 675 declined to participate. The final SPARC population therefore consisted of 588 participants (47% of those eligible), who consented to multimodality testing including record review, transesophageal echocardiography (TEE), and carotid ultrasonography. All participants were followed for 5 years after entry into the study.

Transesophageal echocardiography was successfully performed in 577 participants and revealed a PFO in 140 (24.3%) and an ASA in 11 (1.9%). Of the 140 patients with PFO, 6 (4.3%) had an ASA, whereas of the 437 subjects without a PFO, 5 had an ASA (1.1%; $P = .28$). During the median follow-up of 5.1 years, cerebrovascular events (including cerebrovascular disease–related death, ischemic stroke, and transient ischemic attack [TIA]) occurred in 41 persons. Of the 140 participants with PFO, 12 had an ischemic event. No patient with PFO and a subsequent ischemic event had an ASA on TEE. After adjustment for age and comorbidity, PFO was not a significant independent predictor of stroke (hazard ratio [HR], 1.46; 95% confidence interval [CI], 0.74 to 2.88; $P = .28$). Two of the 5 patients with an isolated ASA had a cerebrovascular event, and the HR after adjusting for age and gender was nearly 4 times higher in patients with an ASA (3.72; CI, 0.88 to 15.71) than in those without ASA. However the absolute number of events was very small, and this did not reach statistical significance.

The authors concluded from this prospective population data that after correction for age and comorbidity, PFO was not an independent risk factor for future cerebrovascular events in the general population. The authors note that a larger study might be required to test the stroke risk associated with ASA.

Comment

Stroke occurs in about 500,000 persons in the United States each year (20%-40% are embolic in nature), with an equal number experiencing TIAs. Once a stroke has occurred, the reported recurrence rate ranges from 4% to 14% annually, approximately 30% of which occur in the first 30 days. Because of this high recurrence rate and the fact that 50% of stroke patients will have significant residual physical and functional impairment, there is obvious interest in identifying potentially treatable causes of stroke.

With the advent of TEE, it has become possible to detect left atrial thrombi, left atrial appendage thrombi, and protruding and mobile aortic atheroma that are associated with cerebral embolism. PFO and ASA have also been associated with embolic strokes, but the relationship is more complex and, as noted by Overell and associates in their meta-analysis, "The literature on the prevalence of interatrial septal abnormalities in stroke is both extensive and confusing."[1]

PFO is reported at pathology in approximately 27% of affected patients[1,2] and in approximately 25% by TEE.[3] Therefore, one would expect at least 25% of stroke patients to have a PFO by random association. A meta-analysis of case-control studies reported widely differing PFO detection rates (10% to 44%) for patients with stroke, 31% to 77% for cryptogenic stroke, 4% to 25% for stroke of known cause, and 3% to 22% in controls.[1]

When all patients with ischemic stroke were combined, there was a significant relationship between stroke and PFO (odds ratio [OR], 1.83), ASA (OR, 2.35), and PFO plus ASA (OR, 4.96). However, when the patients were subdivided into those older and younger than 55 years, the association for the older group was no longer significant. When patients with cryptogenic stroke were compared with patients with stroke of known cause, the ORs for PFO, ASA, and ASA and PFO all increased for the whole group and in those patients younger than 55 years. However, they still just failed to reach significance for PFO for the group older than 55 years. This suggests that a true effect may exist that is easier to detect when more common causative factors have been excluded or, as in the younger population, are less prevalent. However, in a prospective study involving 581 patients (aged 18 to 55 years), Mas and coworkers[4] found no difference in the rate of recurrent stroke in patients with PFO alone compared with those without PFO.

As all of these trials deal with stroke after it has occurred, there is an obvious bias in patient selection. Similarly, in studies using TEE as a reference, there is further selection bias, as obviously not all patients with stroke are referred for TEE. The study of Meissner and colleagues is unique in that it prospectively follows a "randomly selected population," only 6.3% of whom had a prior history of cerebrovascular disease before the index TEE. The prevalence of PFO in this study (24.3%) was similar to that expected in a random population. In this prospectively studied population, there was no statistically significant difference in stroke in patients with PFO compared with those without. However, the number of events in the PFO group was small (n = 12) and the patient group was older (mean age, 66.9 years), a population in which other causes of stroke would be expected to predominate. Lock estimated that less than 0.1% of persons with a PFO will have an embolic stroke of "unknown" origin, and thus it will take a much larger group to demonstrate this association.

Conversely, this study serves to emphasize the infrequence of this association. In addition, the study of Meissner and associates cannot address the difference in risk in younger versus older patients, because the number of younger patients is small and the number of events in this group, although unstated, is presumably small also. Thus, although there is clearly some association between the presence of a PFO and embolic stroke based on clinical and pathologic evidence of paradoxical emboli and the echocardiographic demonstration of examples of straddling thromboemboli that have become transiently trapped in the foramen ovale, the incidence of this phenomenon in the general population is small and would require much larger studies to define it clearly. It is also important to remember that the PFO itself is not causative but merely permits venous thromboemboli to pass from the right to the left side of the circulation. Although the present study showed no increased risk in patients with a history of venous thrombosis, the numbers were again small, and presumably this association must occur.

The relationship of ASA and stroke in case-control studies has been more convincing than that for PFO, although again differences in diagnostic criteria between studies make interpretation difficult. In the meta-analysis of Overell and coauthors,[1] the OR for ASA alone for all patients with ischemic stroke was 2.35, compared with 4.96 for those with ASA and PFO. The risk was higher in patients younger than 55 years (OR, 6.14 for ASA and 15.59 for ASA and PFO) and still higher when patients with stroke of known cause were compared with those with cryptogenic stroke. In the study of Mas and coworkers[4] of a selected population of young patients with prior stroke, the presence of both ASA and PFO was a significant predictor of recurrent stroke (HR, 4.17; CI, 1.47 to 11.84), whereas isolated PFO or ASA was not. In the study by Meissner and associates, ASA was also predictive of future cerebrovascular disease, but again, the number of events was small (n = 2), and both events occurred in patients with ASA but no evidence of PFO. Thus, although there is evidence of increased risk of stroke in patients with PFO and ASA, the absolute number of events remains small. Data for ASA alone are conflicting and the mechanism of stroke in these cases is less clear.

In conclusion, the study by Meissner and associates is an important contribution, it is the first attempt to examine this question in a prospective, randomized manner. Their failure to show a relationship between stroke and PFO emphasizes the relatively small risk of PFO in the general population. This is important given the current interest in percutaneous closure of atrial communications. Their study also suggests that much larger numbers of patients would be required to accurately define this relationship and demonstrates the difficulty, if not

impossibility, of recruiting the required number of participants for a study using a relatively invasive method such as TEE as the reference standard. ■

References

1. Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology.* 2000;55:1172-1179.
2. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc*. 1984;59:17-20.
3. Meissner I, Whisnant JP, Khandheria BK, et al. Prevalence of potential risk factors for stroke assessed by transesophageal echocardiography and carotid ultrasonography: the SPARC study. Stroke Prevention: Assessment of Risk in a Community. *Mayo Clin Proc*. 1999;74:862-869.
4. Mas JL, Arquizan C, Lamy C, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. *N Engl J Med*. 2001;345:1740-1746.