Stroke remains one of the most feared and devastating complications for patients to envisage. This remains true regardless of the age of the patient and the presence or absence of comorbidities, but it may be relatively more important the younger the patient is. Establishing the pathogenesis of stroke is fundamentally important for attempts at prevention. In some patients, the diagnosis of the underlying cause is relatively straightforward—e.g., the presence of a high-grade, ulcerated lesion in the carotid artery in the distribution of the central nervous system symptoms or neurological deficit. In other cases, it may be considerably more difficult; then, the question of a cardiac source is often raised.

Echocardiography has become an integral part of the evaluation in many such patients. Early in the history of this field, attention was focused on the left atrial appendage as a putative source. In addition, however, abnormalities of the atrial septum were documented and have since come to occupy an important position. These abnormalities were further characterized after the introduction of contrast studies and transesophageal echocardiography, which helped in the documentation of patent foramen ovale (PFO), atrial septal aneurysm (ASA), and right-to-left shunt. In such patients, emboli potentially could pass from the venous to the systemic arterial circulation. It must be remembered that there may be other mechanisms, including thrombus forming in the ASA or thrombus from supraventricular arrhythmias. In a recent meta-analysis, there were 2738 references of case-control studies that identified the keywords PFO, ASA, or right-to-left shunt. In this meta-analysis, combined odds ratios were calculated with the use of both fixed and random-effect methods. There are several important issues that can be addressed, including: (1) the frequency of each of these conditions in control populations versus patients with cryptogenic stroke or stroke of known cause; (2) the relationship between septal abnormalities and stroke rates with some inference as to causality versus association; and (3) the role of anticoagulant or antiplatelet therapy or both for prevention. These issues form the background for the closure devices.

There are several take-home messages to be learned from the literature, which are highlighted in the meta-analysis as well as in single series. These messages include: (1) Abnormalities of the atrial septum occur in normal control patients, patients with cryptogenic stroke, and those with stroke from other putative causes. (2) Patients with combined abnormalities (both PFO and ASA) have a higher incidence of ischemic stroke. (3) The patient’s age is an important discriminant factor: In patients aged <55 years, the odds ratio of ischemic stroke versus control subjects was 3.10 (95% confidence interval [CI] 2.29 to 4.21) for PFO, 6.14 (95% CI 2.47 to 15.22) for ASA, and 15.99 (95% CI 2.83 to 85.87) for combined ASA and PFO. For patients aged >55 years, the odds ratio was 1.27 (95% CI 0.80 to 2.10) for PFO and 5.09 (95% CI 1.25 to 20.74) for PFO plus ASA. Homogeneous results were usually seen from study to study in patients aged <55 years, but heterogeneous results were seen in older patients. Accordingly, the conclusion can be reached that in patients aged <55 years, PFO and ASA are associated with ischemic stroke, and some causality can be inferred if no other causes are identified. In patients aged >55 years, the association, and in particular causality, is much less clear because of the number of other possible causes.

With the establishment of the potential relationship or association in any specific patient or groups of patients, the next obvious step moves to prevention of a recurrent event. Several approaches have been used, including antiplatelet strategies, anticoagulant strategies, surgical closure, and, now, percutaneous approaches.

Antiplatelet or anticoagulant therapy has been the focus of several studies. Mas et al recently reported 581 patients aged <55 years treated with 325 mg aspirin daily for secondary prevention after an ischemic stroke of unknown pathogenesis that had occurred within the preceding 3 months. They found in this group of 581 patients that 216 had a PFO alone and 51 had both a PFO and an ASA. In these 2 groups, the risk of recurrent stroke at 4 years was 2.3% in the former (95% CI 0.30 to 4.30), whereas it was 15.2% (95% CI 1.80 to 28.60) in the latter. It is interesting to note that in patients with no atrial septal abnormality, the risk of recurrence was 4.2% (95% CI 1.8% to 6.6%). Accordingly, the authors concluded that in younger patients with a prior ischemic stroke with combined PFO and ASA, aspirin is an inadequate preventive strategy. This is in contrast to those patients with only a PFO, in whom there is no increased risk of recurrence while on aspirin.

Anticoagulant therapy has also been studied in the setting of a multicenter trial. Homma et al reported on 630 stroke

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patients randomized to either warfarin or aspirin. Of those patients studied, 203 had a PFO. The patients had a mean age of 57.9 years. The primary end point was recurrent ischemic stroke or death from any cause. This primary end point at 2 years occurred in 15.4% of the patients without a PFO, 18.5% with a PFO, and 9.5% with a large PFO. The hazard ratio was not significant, regardless of whether the PFO was large or small or whether warfarin or aspirin was used. There was no significant difference in the time to recurrent stroke or death between patients with and those without a PFO. It is important to note that the mean international normalized ratio in patients on warfarin was 2.04. Accordingly, the authors concluded that, “on medical therapy the presence of a PFO in stroke patients did not increase the chance of adverse events irrespective of PFO size or the presence of atrial septal aneurysm.”6

Surgical approaches have also been reported, again with some mixed results.9–11 Obviously, the risk of surgery needs to be considered in the equation, although in a recent series, Dearani et al10 had no operative mortality although some were aged /H11349/H11006/H11006/H11006 average of 1.4 /H11021/H11021 years, with 25% having a history of multiple emboli in the past, an average of 1.4±0.7 episodes per patient. In general, the patients were young, with a mean age of 47±14 years, although some were aged ≤77 years. We might expect that, as previously described, patients aged <55 years would fare better in terms of subsequent episodes after closure of the defect.

Only 2 devices were used, the Sideris Buttoned device or CardioSeal Occluder. From the standpoint of the initial procedure, the outcome was excellent with successful device deployment in all patients and no mortality but some morbidity, including 1 device migration requiring surgery and 1 tamponade. Full and complete PFO occlusion (evaluated by bubble study) was only achieved in 44% initially, but that number grew during follow-up to 77%. The device was not perfect, however, inasmuch as 2 patients had recurrent neurological events and 4 (3.6%) required repeat intervention during the mean follow-up of 2.3 years. Still, at 5 years, Kaplan-Meier analysis documented that 90% of patients were free from either recurrent emboli or reintervention.

There are several important issues to be considered: (1) Just because a device is implanted does not mean that all antplatelet or anticoagulant therapy can be stopped. This therapy needs to be continued until the device has endothelialized, which usually takes ∼3 to 6 months but may be longer, as some studies have documented increased events within the first year.14 In some patients, more intensive antplatelet or anticoagulant therapy may be required during this time. (2) Just because a PFO is present does not mean that closure of it will prevent further events if the pathogenesis is not related to either the PFO or the ASA. (3) Patient selection criteria will continue to evolve and are extremely important, paying great attention to evaluating and ruling out other causes. (4) At the present time, the devices available are approved for closure of atrial septal defect and ventricular septal defect; they are not approved for a PFO indication. They are used as an off-label indication or under the auspices of the Humanitarian Device Exemption. The latter requires that certain conditions be met, namely, that the patient has a recurrent event on treatment. Does that mean the patients must have a stroke before qualifying for a device? Does that mean the patients must have a recurrent stroke before qualifying for such a device? Both of these questions involve important clinical and ethical issues. (5) Finally, what will be required for an approvable indication? Typically, the Food and Drug Administration requires a randomized trial. If so, what will the patient population be (eg, cryptogenic stroke any age, failed antplatelet therapy, PFO or PFO plus ASA) and what will be the control group (surgical closure, dual antplatelet therapy)? These are important issues that will affect patient care and clinical outcome.

At the end of the day, we are left to decide whether or not Mother was right; do we always need to close the door to keep something either out or in, according to the situation? Obviously, the answer to this is complex—and depends in this situation on whether the material causing the central nervous system symptoms is coming from right to left through the door (atrial septum) or from a very different source. What can be said from the standpoint of PFOs and ASAs is that (1) they do exist and are common, and (2) closure is reasonable in patients who have had an ischemic event that is cryptogenic (particularly in young patients). Whether it is absolutely better than prolonged anticoagulant or antplatelet therapy or some combination is as yet undetermined.

References


**KEY WORDS:** Editorials ■ stroke ■ pathology ■ heart defects, congenital ■ cerebral ischemia
Was Your Mother Right—-: Do We Always Need to Close the Door?

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