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Editorial Comment

The Case for Closing PFOs

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The significance of a patent foramen ovale as the culprit pathway for a cryptogenic stroke is a fascinating concept that is gaining acceptance. When this idea was first proposed, it was greeted with skepticism in the scientific community. The likelihood that a blood clot from the lower extremities could enter the right atrium just at the moment when a patient produced a spontaneous valsalva maneuver to open a patent foramen ovale and push the embolus into the left atrium was thought to be extremely remote. However, there are two pieces of evidence that suggest this indeed may be the major physiologic mechanism of cryptogenic stroke. The first is that the incidence of a PFO (diagnosed by TEE) is present in only 10%–23% of the population, whereas the incidence of a PFO in patients who have had a cryptogenic stroke is estimated at 40%–70% [1–4]. The second finding is that recurrent stroke is nearly eliminated in patients who have the PFO closed [5]. In addition, isolated cases have been described by echocardiography, where a thrombus was seen straddling a foramen ovale. It is clear from these examples that thrombus can pass across a PFO. What is uncertain is how often this event occurs. Jim Lock, who pioneered PFO closure in 1989, has proposed an additional mechanism to explain how a PFO could be a causal factor in cryptogenic stroke. He suggests that the PFO acts more like a tunnel rather than a hole or flap. Since there is usually stasis within this tunnel, a thrombus may develop in situ within the PFO and subsequently is pushed into the left atrium when the patient bears down. This potential mechanism would address the concerns of those who are daunted by the probability of a venous thrombus spontaneously crossing the PFO on its voyage through the right side of the heart. A rough estimate of the magnitude of this problem is enlightening. The number quoted by the American Stroke Association for people suffering a symptomatic stroke each year in United States is 1 million. Of these, 80% are ischemic, 20% are hemorrhagic. The Stroke Center at UCLA estimates that 20% of these 800,000 ischemic strokes are cryptogenic. Of the estimated 160,000 cryptogenic strokes per year, approximately 40%–70% have PFOs. The estimated number may depend on how aggressive the evaluation has been. This yields approximately 60,000–110,000 strokes per year in which PFO is the leading identifiable cause. In addition, recent population studies using MRI screening suggest that there may be up to 11 million Americans per year who suffer a silent stroke. Since transesophageal echocardiogram studies were not performed in this patient population, we do not know what the incidence of PFO is in these patients with asymptomatic strokes. The potential volume of patients at risk is disturbing (Jeffrey Saver, UCLA Stroke Service, personal communication). With the availability of the CardioSEAL device used under the Humanitarian Device Exemption regulations of the FDA, percutaneous closure of PFOs in patients with cryptogenic stroke has increased. Approximately 4,000 devices have been deployed in the past 3 years. It is unfortunate that no

randomized trial of medical therapy vs. a closure device has been performed. It is also unlikely that such a study will be undertaken since these patients are extremely reluctant to participate in a protocol that might randomize them to receive prolonged anticoagulation, a treatment with known risks and limited evidence of efficacy in this condition. These people are terrified of sustaining another stroke. In this issue, Du et al. describe their results in 18 patients who received a catheter-based closure of a PFO using either a Das Angel-Wings occluder or an Amplatzer device. With a mean follow-up of 1.6 years, there was no evidence of recurrent embolic events. This is reassuring but the number of patients is too small to overstate the success of this procedure. Larger series using different devices have reported a subsequent embolic event rate of 3.2%/year in 63 patients [6] and 3.4% in 80 patients [7]. It is possible that this represents an early experience with devices that may not have completely occluded the interatrial pathway. A more recent study in 91 patients reported no strokes and two TIAs at 7 months (personal communication, Paul Kramer). Some surprising results of the WARSS (Warfarin Aspirin Recurrent Stroke Study) are pertinent to this issue. This study compared aspirin (325 mg/day) with warfarin (INR 1.4–2.8) for the secondary prevention of stroke. Patients with obvious causes of stroke such as symptomatic carotid stenosis or cardioembolic stroke were excluded from the study. Of the 2,206 patients enrolled in the study, the rate of recurrent ischemic stroke or death at 2 years was 17.8% in the warfarin-treated patients and 16.0% in the aspirin-treated patients. The fact that there was no significant difference between aspirin and warfarin is important; what is disturbing is the very high recurrence rate in these patients with cryptogenic stroke despite either form of therapy. Deployment of these devices is not technically difficult for operators who are used to performing coronary angioplasty, but there is a learning curve to precise placement and unusual complications may occur such as air embolus. These issues are problematic but they are technical and can be solved. There are also other questions that need to be addressed for catheter-based closure of PFOs: How to deal with large atrial septal aneurysms? Which approach is best, trans-PFO or transseptal puncture? Should general anesthesia be used? Is ultrasound guidance with a transesophageal or intracardiac echo preferable? How frequent are false negative bubble studies which may underestimate the incidence of PFO associated cryptogenic stroke? What is the incidence of thrombus forming on the device and producing recurrent embolism? This is a very exciting area that is ripe for clinical investigation. The potential for preventing large numbers of strokes in young patients is impressive. It would be a great opportunity for NIH to sponsor a randomized controlled study of these issues.

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