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Editorial

Patent Foramen Ovale: Paradoxical Embolism and Paradoxical Data

With the use of contrast-enhanced transesophageal echocardiography (TEE), a right-to-left intracardiac shunt via a patent foramen ovale (PFO) is detected frequently during evaluation of patients with an ischemic stroke. During the past 20 years, an association of PFO with stroke, migraine headache, and decompression-induced neurologic dysfunction has been suggested.¹⁻⁴ Presumably, most of the neurologic symptoms are secondary to paradoxical embolism of small thrombi that arise in the venous system and pass through the PFO during a transient right-to-left shunt; however, cases demonstrating a thrombus traversing the PFO are relatively few.⁵⁻⁷ Other possible explanations for stroke secondary to PFO but independent of paradoxical embolism include secondary cardiac arrhythmias or abnormalities of the endocardial surface of the septum or within the PFO that are a focus for thrombus formation.^{8,9} In summary, the mechanism of stroke among persons with PFO is ill-defined, and some other as yet unknown confounding factor might explain any association.^{10,11} In addition, some causes of paradoxical embolism can be secondary to extracardiac right-to-left shunts, such as a pulmonary arteriovenous malformation.¹²

In the current issue of the *Mayo Clinic Proceedings*, Earing et al¹³ describe the utility of intracardiac guidance, using echocardiography, during transcatheter placement of devices to occlude a PFO. Khositseth et al¹⁴ describe their experience with placement of intracardiac occlusive devices in 103 patients with presumed paradoxical embolism. In addition, Horton and Bunch¹⁵ address several issues

Dr Adams is an investigator in CLOSURE, a trial sponsored by NMT Corporation, which is comparing the placement of closure devices to best medical treatment for patients with PFO. The views expressed herein are those of the author and do not necessarily reflect those of the sponsor or the other investigators.

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related to the diagnosis and treatment of patients with cerebral infarction and PFO. These articles are timely because of the considerable interest, within the cardiology community, in the importance of PFO.

Some cardiologists estimate that 60,000 to 110,000 strokes are secondary to paradoxical embolism via a PFO.^{16,17} Besides preventing stroke, transcatheter closure of PFO has been proposed as a prophylactic treatment for migraine headache.¹⁸ However, questions persist. Much of the current evidence is circumstantial or anecdotal. Reports about the potential utility of medical or surgical interventions are from uncontrolled studies, which can be biased. When the rules of evidence are used, these studies provide data of modest strength. Of note, evidence from prospective clinical studies has not matched our preconceived notions.^{19,20} Specifically, the risk of stroke might not be as high as previously believed, and relatively conservative medical therapies might be effective. Because of reservations about the robustness of the current data, many neurologists are uncertain about the cause-and-effect relationship between PFO and stroke and about the best management of patients.

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This commentary poses a series of questions and includes currently available data; it also serves as a springboard for further discussions.

What Is the Association Between PFO and Cerebral Infarction?

Depending on the criteria used for diagnosis and the technology used in cardiac assessment, the prevalence of PFO in the healthy population is approximately 20% to 25%.^{16,21,22} On the basis of this prevalence, we can estimate that approximately 60 million to 70 million Americans have a PFO. Thus, detection of a PFO during the evaluation of a patient with stroke is not surprising, and the frequency

of PFO detection in these patients can be as high as 40% to 45%.^{1,23}

Overell et al² concluded from a meta-analysis of several studies that the relative risk (RR) of stroke compared with non-stroke controls increased by a factor of 1.83 (95% confidence interval [CI], 1.25-2.66) if a PFO was present. They also found that if an atrial septal aneurysm (ASA) was present, the RR was 2.35 (95% CI, 1.46-3.77) and that if both ASA and PFO were present, the RR was 4.96 (95% CI, 2.36-10.39). These data suggest that the presence of a PFO denotes a patient who is at increased risk for cerebral infarction. However, the statistical association does not automatically establish a cause-and-effect relationship.¹⁰ For example, data could be biased by patient referral or evaluation. The indications for ordering a TEE vary among physicians; for example, a cardiac imaging study might not be performed if another etiology of the stroke has been elucidated already. The frequency of detection of PFO is especially high among persons without another obvious explanation for the stroke (ie, cryptogenic stroke). This association probably is correct, but caution must be exercised. Physicians evaluating a patient might be more likely to do cardiac imaging, including contrast-enhanced TEE, if another cause for stroke is not obvious.

Patients with PFO usually are younger and have a lower frequency of hypertension, hypercholesterolemia, and smoking than do persons with other causes of stroke.^{16,23} On the basis of an analysis that combined the results of several other studies, Overell et al² found that for stroke associated with PFO among persons younger than 55 years, the RR was 3.10 (95% CI, 2.39-4.21). For ASA, the RR was 6.14 (95% CI, 2.47-15.22); for the combination of ASA and PFO, the RR was 15.59 (95% CI, 2.83-85.87). The data suggest that the importance of PFO in the pathogenesis of cerebral infarction probably is greatest among young adults. However, these observations also might be subject to bias because cardiac imaging is done most frequently among young persons. Although PFO can be found in older patients,^{21,24} these persons have a high prevalence of atherosclerosis or other cardiac diseases, including atrial fibrillation, which might explain their vascular events. Thus, a PFO might not be perceived as being as important in an older person as in a young adult.^{2,22}

Additional epidemiological or population-based studies are needed to establish the potential relationships between PFO and stroke. In particular, the importance of age to the relationship between PFO and stroke needs to be clarified.

What Are the Requirements for Diagnosing Paradoxical Embolism Secondary to PFO?

A recent history of deep venous thrombosis buttresses the diagnosis of paradoxical embolism.¹¹ Because symp-

tomatic venous thrombosis is not a common phenomenon among otherwise healthy young adults, a potential interaction with an acquired or inherited hypercoagulable disorder should be considered. Such interactions have been proposed among patients having antiphospholipid antibodies, prothrombin gene mutation, or factor V Leiden mutation.²⁵

The attribution of a cerebral infarction to paradoxical embolism is strengthened by the presence of a venous source for the clot. When paradoxical embolism is the presumed mechanism of stroke, the patient can be evaluated to look for a thrombus arising in the pelvis or the deep veins in the lower extremities. Because the emboli might be tiny, the original clot also might be extremely small, and its detection could be difficult. Not surprisingly, evaluation of the veins has a relatively low yield. Although Lethen et al²⁶ found deep venous thrombosis in approximately 10% of their patients, Ranoux et al²⁷ found latent venous thrombi in only 4% of their patients. Lamy et al²³ found no relationship between venous thrombosis and stroke among patients with PFO. Thus, the presence of a predisposing venous thrombus is inferential, and this component for diagnosis of paradoxical embolism cannot be established in most patients. Still, the inability to detect a venous thrombus does not eliminate the possibility that paradoxical embolism occurred.¹¹

Presumably, paradoxical embolization requires that the right atrial pressure exceeds that found in the left atrium. Additional research is needed on the changes in right and left atrial pressures among persons with PFO. In an experimental model, Black et al²⁸ found that mean right and left atrial pressures are poor predictors of right-to-left intracardiac shunting. This report suggests that pressure gradients differ markedly during various phases of the cardiac cycle. However, circumstances that would increase right atrial pressure presumably also might be required for the right-to-left shunt to occur at the time of paradoxical embolism. Coughing, straining at stool, lifting, or any other Valsalva maneuver, which would transiently increase right atrial pressure, might provide the circumstances to promote paradoxical embolism. Although historical information linking stroke to such activities can be obtained from some patients, Lamy et al²³ could find no consistent link between stroke and a Valsalva maneuver. Thus, the temporal sequence between stroke and a transient right-to-left intracardiac shunt is difficult to establish in most patients.

Because most persons with PFO never have symptoms, some lesions can be assumed to be associated with greater risk than others. Establishing a relationship between the size of the septal abnormality, a concomitant ASA, the presence of a shunt at rest, or the size of the right-to-left shunt might identify those persons at highest risk. The Valsalva maneuver or coughing is used often to transiently increase pressure in the right atrium to detect a transient

right-to-left shunt. A right-to-left shunt is considered present if microbubbles are detected within 3 to 5 cardiac cycles.¹⁵ The volume or number of bubbles is used frequently to quantify the size of the shunt. Presumably, the volume of bubbles can serve as the surrogate for the size of the PFO.²⁹ However, the criteria for grading the size of the shunt are arbitrary.¹⁵ Also, correlations between the size of the right-to-left shunt and the risks of stroke are not strong. A large multicenter study found no relationship between the size of a shunt and the risk of recurrent stroke.²⁰ De Castro et al³⁰ reported that right-to-left shunting present at rest was associated with a high risk for embolic events, a relationship that makes sense intuitively; however, more supportive information is needed. In addition, Cabanes et al³¹ found that both interobserver agreement and intraobserver reproducibility in diagnosing PFO or ASA by TEE were disappointing.

Because of the lack of a consistent correlation of the size of the shunt with the risk of embolization, other methods to quantify the severity of the PFO and presumably the attendant risk for embolization are being examined. Schuchlenz et al³² evaluated PFO size in a series of patients who subsequently underwent catheter closure of the defect. They found that the balloon diameter of the PFO was considerably larger than the diameter estimated by TEE. They also reported that a PFO diameter greater than 4 mm was associated with increased thromboembolic risk.³³ These findings are interesting, but additional data are needed.

De Castro et al³⁰ noted a strong correlation with the risk of embolization when a PFO is associated with a highly mobile septal membrane and speculated that the flapping motion of the ASA might direct small clots coming from the inferior vena cava into the defect. This finding is supported by other studies that found that a highly mobile interatrial septum (ASA) is associated with PFO, large right-to-left shunts, and an increased risk of stroke.³⁴⁻³⁶ The strongest data supporting a high risk of embolization among persons with PFO and ASA were reported by Mas et al.¹⁹ In contrast, a multicenter American study found no relationship between the presence of an ASA and stroke among persons with a PFO.²⁰ Although current information suggests that the combination of an ASA and PFO is more dangerous than an isolated PFO, additional data are needed to establish such a link.

The subgroup at high risk for paradoxical embolization needs to be consistently identified. Further, this subgroup needs to be identified using technology that has a high degree of specificity, sensitivity, and reliability.

What Is the Risk of Re-embolization Among Patients With PFO?

One analysis suggests that the annual risk of recurrent transient ischemic attack or stroke is approximately 3% to

16% and that the presence of the cardiac abnormality increases the risk of stroke by approximately 5 times.¹⁶ Such a figure is alarming. However, in a large French study, Mas et al¹⁹ prospectively evaluated the rates of recurrent stroke among young adults with cryptogenic stroke and PFO who were treated with aspirin. At 4 years, recurrent strokes had occurred in 2.3% of patients with PFO, a lower rate than the 4.2% noted among patients who had no cardiac abnormality identified. Homma et al²⁰ found no increase in stroke risk that could be ascribed to the PFO. If these data and those from the French study are correct, and currently they are the best data available, the risk of recurrent embolic stroke among patients with PFO does not seem to be unusually high. The cardiac lesion might not be particularly dangerous. In addition, long-term studies examining the long-term risk of recurrent embolization have not been done. Knowing whether the likelihood of new ischemic events declines over time could influence decisions about prevention. For example, long-term treatment with oral anticoagulants might be unnecessary if the chances of stroke decline after the first few months or years after the original event.

Mas et al¹⁹ reported that the 4-year risk of stroke among young adults with PFO and ASA was 15.2%. However, these data need to be viewed with care because the CIs showed that the actual risk could be anywhere from 1.8% to 28.6%. In addition, Homma et al²⁰ found no increased risk of recurrent embolization among patients with PFO who also had an ASA. On the basis of these data, caution should be exercised about assuming that the combination of ASA and PFO is especially dangerous. More information is needed about the stroke risk associated with the presence of increased septal mobility among persons with PFO.

At present, the data about the risk of recurrent embolization are paradoxical. The risk could be as high as 16% or as low as 0.6%. The former figure implies that a PFO is a dangerous lesion that warrants aggressive therapy; the latter figure suggests that a PFO is not a particularly ominous finding. If the former estimate is accurate, physicians can justify recommending medical or surgical interventions that might be associated with serious complications because the risk-benefit ratio favors treatment. Conversely, if the risks are low, recommending any intervention associated with a risk higher than that of aspirin would be difficult to justify.

What Are the Treatment Options for Patients With Stroke and PFO?

Regardless of the presence or absence of a PFO, the perceived risk of recurrent stroke among patients with symptomatic ischemic cerebrovascular disease is sufficiently high that some stroke prophylaxis regimen should

be prescribed. The choices of antiplatelet aggregating agents, oral anticoagulants, transcatheter placement of an occlusive device, or cardiac surgery present a broad range of options that entail different risks and vary considerably in economic costs. For example, Baker et al³⁷ estimated that the per-patient cost of an occlusive device is approximately \$7500 and for direct surgical closure of an atrial septal defect is approximately \$15,000. Thus, clear evidence about the utility of each of these therapies, probably in comparison with aspirin prophylaxis, is needed. Such information is important for patients, physicians, and third-party payers.

Oral anticoagulants often are recommended based on the assumption that the thrombi are arising in the venous system and because oral anticoagulation is the preferred medical regimen for preventing embolism among patients with high-risk cardiac lesions. The only trial to test oral anticoagulants (desired international normalized ratio of approximately 2) was the PFO in Cryptogenic Stroke Study (PICSS).²⁰ No statistically significant difference in mortality or frequency of recurrent stroke was noted between patients treated with adjusted-dose warfarin or aspirin at 300 mg/d. The results of PICSS buttress those reported by Mas et al.¹⁹ With aspirin treatment, the frequency of recurrent stroke among patients with PFO was 2.3%. Although this study did not compare aspirin with warfarin, it reports an extremely low rate of recurrent embolic events during treatment with the antiplatelet agent. Despite the expectation that warfarin would be superior to aspirin in preventing recurrent stroke, presumably secondary to paradoxical embolism among patients with PFO, no data currently are available to support this assumption. Until such data become available, a reasonable assumption is that the role of these medications is limited to treating patients with a proven venous thrombus or coagulopathy.

Mechanical closure of the PFO, an alternative to antithrombotic therapy, has been proposed as the definitive way to prevent recurrent paradoxical embolism. One of the main reasons for local interventions has been to eliminate the need for long-term (possibly lifetime) anticoagulation. Several small series of direct surgical closure of the PFO have been reported³⁸⁻⁴⁰; however, because of the relatively small number of patients who underwent this procedure, good estimates of operative morbidity are not available. Potential complications include cardiac arrhythmias, pericardial effusion, bleeding, wound infection, intra-atrial thrombi, and stroke. The surgery might be particularly dangerous if a patient has had a recent stroke.¹¹ In addition, the long-term success of surgery has not been established. Meier and Lock¹⁶ estimated that the likelihood of recurrent stroke after surgery could be 4% to 20% and concluded that surgical PFO closure has been supplanted by placement of

devices. Conversely, Ruchat et al³⁹ concluded that surgery is the option of choice for selected patients at high risk for stroke. The data required to support this conclusion are not obvious. Some carefully selected patients might benefit from surgery, but currently the features that would necessitate direct operative closure are not known. With the advances in transcatheter placement of closure devices, the role of major cardiac surgery seems to be diminishing. Most patients with PFO probably do not need the potentially dangerous open heart operation.

The enthusiasm for transcatheter placement of an occlusive device to seal a PFO is considerable. The procedure has several advantages. It can be done on an outpatient basis using local anesthesia and usually takes less than 30 minutes. Technical advances are improving the procedure,¹³ and because of the rapidly evolving technology, safer devices are being developed. In general, technical failures are rare, and the PFO can be closed completely in approximately 95% of patients.^{14,16,41,42} These devices may lower the long-term risk of recurrent embolization.

In the current issue of the *Mayo Clinic Proceedings*, Khositseth et al¹⁴ reported that the average annual recurrence of all embolic events was 3.6% and speculated that recurrent stroke could occur in the absence of a residual intra-atrial shunt. They concluded that closure of the PFO is safe and effective. However, complications of device closure do occur. Berdat et al⁴³ reported that surgical interventions to manage complications of transcatheter procedures were needed in 8% of patients. Cases of thrombus formation on the device, cardiac perforation, infective endocarditis, and other events requiring surgery have been reported.⁴⁴⁻⁴⁹ Thus, although the risk of major complications of transcatheter closure of PFO appears to be low, the procedure is not risk-free.

Closure of a PFO does not mean that further strokes will be prevented, particularly if the cause of the stroke has no relationship to the septal defect.²² Placement of a device does not mean that all antithrombotic agents can be halted.²² Patent foramen ovale closure will not prevent pulmonary embolism among patients with deep venous thrombosis.¹¹ No benefit-risk ratio for transcatheter closure has been established.⁵⁰ The benefit of the occlusive procedure has not been shown because no data are available about the utility of transcatheter PFO closure compared with medical treatment.

What Is the Status of Managing Patients With Stroke and PFO?

Considerable uncertainty exists about the management of patients with PFO and stroke.^{9,11} At present, no particular therapy can be recommended for asymptomatic patients with PFO.⁵¹ Rosin⁵⁰ concluded that none of the therapeutic

options could be recommended if the rules of evidence are used to assess the current data. This conclusion is correct. At present, no data prove that any medical or surgical intervention is superior to aspirin.²⁰ To date, no trial has tested either transcatheter or surgical closure compared with medical management.⁵¹ Trials are needed to determine the indications and limitations of these surgical procedures.¹¹ Tobis¹⁷ concluded that clinical trials probably could not be done because of patient reluctance to participate, either from fear of recurrent stroke (unless the PFO is closed) or from fear of bleeding complications from anticoagulants. We hope that Tobis' prediction will be wrong because patients and their doctors need to know whether these closure devices are needed.

We cannot assume that all patients with PFO and neurologic symptoms need to have the cardiac abnormality corrected. Some patients might benefit substantially from closure of their PFO; however, the procedure might be unnecessary in other patients. The neurology and cardiology communities need to collaborate in clinical studies to prospectively test the safety and efficacy of PFO closure devices.

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