

EDITORIAL COMMENT

Patent Foramen Ovale: Friend or Foe?*

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Transesophageal echocardiography (TEE) has been increasingly used for the evaluation of patients with a suspected cardiac source of embolization (1). Transesophageal echocardiography findings such as spontaneous echocardiographic contrast, atrial septal aneurysm (ASA), patent foramen ovale (PFO), aortic atheroma, left atrial thrombi, and cardiac masses have been related to an increased risk of embolization (2–8) based on a higher prevalence in patients with suspected embolism compared with those who underwent TEE for other reasons. These findings have also been useful to risk-stratify patients with atrial fibrillation (9,10). In the last 15 years, significant efforts have been made to understand the clinical significance of these findings and to identify the optimal treatment (11–16).

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The management of patients with PFO is controversial. Early transthoracic studies suggested that the prevalence of PFO was high in the general population (25% to 33% of all individuals) but significantly higher in younger patients with cryptogenic stroke (17–19). Recent case-control studies have shown that in patients <55 years old, the prevalence of PFO is three times greater in patients with suspected ischemic events and that the presence of ASA is six times greater than in the general population (15). Mechanistic hypotheses have been postulated, including paradoxical embolization of thrombi from the peripheral venous system, direct embolization from thrombi formed within the interatrial septum, particularly in those with ASA, and concurrent association of right atrial (RA) abnormalities, such as the Eustachian valve and Chiari network (20–22).

There is a significant association of ASA and PFO both in large cohort populations and in patients with suspected cardiac source of embolization (23,24). Atrial septal aneurysm is associated with right-to-left interatrial shunting. In addition, patients with PFO who have an associated ASA are thought to be at higher risk of embolization (25).

The Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS) included 630 patients with stroke adjudged non-cardioembolic who underwent TEE voluntarily or for clin-

ical reasons. All patients were part of the Warfarin Aspirin Recurrent Stroke Study (WARSS) (26). From this population, Homma et al. (21), in this issue of the *Journal*, attempted to identify the mechanism for the increased stroke risk in patients with ASA and PFO. They also assessed the efficacy of medical therapy for preventing stroke recurrence or death in patients with ASA, PFO, and a RA anatomy predisposing to paradoxical embolization. The current study is an extension of previous data published by the same group (16). They found that a large PFO and prominent Eustachian valve or RA filamentous strands were more frequent in patients with ASA than those without ASA (21). After two years of follow-up with treatment of warfarin or aspirin, patients with ASA and PFO had no significant difference in time to recurrent stroke or death compared with those with neither finding (15.9% vs. 14.5%, hazard rate 1.08). Likewise, predisposing RA anatomy posed no risk in excess of the risk borne by those without it. Among patients with PFO and ASA, there was no significant difference in time to recurrent stroke or death between warfarin and aspirin (16% vs. 15.6%; hazard rate 1.0). Previous data supporting an ominous effect of RA anatomy in patients with interatrial abnormalities are soft at best (27,28), and that was confirmed in the study.

These results are in marked contrast with several other studies that have demonstrated that PFO, size of PFO, and the presence of ASA confer higher risk of stroke, primarily in younger patients. In a recent multicenter prospective European study that included 581 patients with ischemic stroke, the recurrent stroke rate for patients with ASA and PFO was 15.2%, versus 4.2% among patients with neither abnormality (25).

Thus, the current results should be interpreted with caution. The patient population in PICSS is not representative of the PFO population in general or of the PFO population with ischemic stroke. The parent study, WARSS, excluded ischemic stroke patients with an inferred cardioembolic source (26). The PFO population in PICSS would not contain patients with a PFO identified before WARSS entry for whom the PFO was considered to be causally related to the qualifying ischemic stroke. These patients could be considered “asymptomatic” with regard to the PFO. The patients who had a PFO identified by TEE after WARSS entry were apparently not highly suspect for harboring a causal or “symptomatic” PFO, because the TEE was not performed during the evaluation for the WARSS-qualifying stroke. In contrast, the retrospective studies showing high risk for PFO and ASA included selected patients at higher risk for cardioembolic source because they were deemed to require TEE as part of their evaluation for stroke. The differences in the PICSS results and prospective studies showing high risk for PFO and ASA in patients with cryptogenic stroke are unexplained, but patient population differences are likely important, as well as the criteria to classify a stroke as cryptogenic. In the largest prospective

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study of stroke patients ages 18 to 55, none of the patients with PFO was excluded from the cryptogenic group. The combination of ASA and PFO was a marker or recurrent stroke—but not the presence of PFO or ASA alone (25).

What are the implications for management from these results? As Dr. Halperin and Fuster (20) pointed out in a similar editorial discussing this group's previous article, the lack of superiority of warfarin over aspirin in the PICSS is indirect evidence that thromboembolism related to atrial arrhythmias or venous disease may not be the predominant mechanism of stroke in patients with PFO. First, the diagnosis of PFO-mediated paradoxical embolism remains presumptive, and cryptogenic embolism is not necessarily synonymous with paradoxical embolism. Second, both PFO and cryptogenic stroke may coexist without causal relation, and such patients would have a low recurrent stroke rate. Third, other mechanisms, such as a genetic predisposition or "paradoxical" crossing of vasoactive substances that would otherwise be deactivated in the pulmonary circulation, cannot be eliminated. The increasingly recognized association of migraine and PFO and its resolution after PFO closure supports this hypothesis (20,29).

The study results imply that medical therapy alone may be protective against recurrent stroke and death in patients with non-embolic stroke. They also suggest that the benefits of a mechanical (surgical or percutaneous) approach to treatment of PFO may be difficult to demonstrate because of a low recurrent event rate with anti-thrombotic or anti-platelet therapy alone. Although the mechanical approach has been safe and effective in uncontrolled studies (30,31), adverse events can occur after surgical correction, such as atrial fibrillation, post-pericardiotomy syndrome, and even stroke (32,33). Percutaneous closure has shown encouraging results, and the newest devices offer promise for low procedural morbidity and long-term durability (30,34) but must be compared with the best medical therapy before this form of management can be recommended as standard of care. Comparisons to medical treatment studies are hampered by the patient selection. Most medical treatment studies include patients with only one previous ischemic embolic episode. On the contrary, percutaneous PFO closure appears to be particularly successful in the subgroup with multiple prior embolic events (30,31).

These interventional studies speak to the dilemma of management of patients with stroke in whom a PFO or ASA is identified. Patients in the interventional studies were thought to be "symptomatic" from the PFO. The stroke patients in PICSS with PFO were "asymptomatic" or, at the least, judged to be non-cardioembolic. With carotid artery disease, the presence of stenosis or the anatomic or hemodynamic characteristics of the carotid stenosis are much less important than whether or not the artery is judged to be symptomatic. Symptomatic status is the major determinant of recurrent stroke on medical therapy, and of the risks or the long-term benefits of non-medical therapies (carotid endarterectomy or stent

(35,36). For patients with PFO, determining symptomatic status in the setting of stroke continues to be a diagnostic challenge. Up to 40% of stroke patients may be classified as cryptogenic, but some of these are likely cardioembolic. Likewise, for some patients with an ischemic stroke, a PFO thought to be "cardioembolic" might be innocent or at least non-causally related to the stroke. This overlap may result in inappropriate patient management, particularly if the stroke adjudication is utilized to guide therapy.

For PFO and ASA, what are the criteria to be used in assessing whether the lesion is causally related to the stroke? What makes a PFO symptomatic? Demonstration of hypercoagulable states and detection of stasis-related thrombi in the peripheral venous system are important (20,37). In those patients, warfarin is likely to be more useful than anti-platelet agents. Recurrent ischemic stroke without other identifiable cause could be another criterion, and for these patients either warfarin or, particularly for patients with recurrent events receiving medical therapy or those with contraindications to anticoagulation, percutaneous closure should be considered. The PFO size, the presence of ASA, and the other anatomic characteristics addressed in PICSS cannot yet be discarded as irrelevant criteria as to whether or not a particular PFO confers increased risk for patients receiving medical therapy. Interventional studies, planned and underway, will include PFO patients who would be excluded from studies of cryptogenic stroke and so will provide data still unavailable regarding the importance of atrial anatomy.

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