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EDITORIAL COMMENT

Is the Hole Only a Part of the Whole?*

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The presence of a patent foramen ovale (PFO) in patients with cryptogenic stroke has generated a rich debate over whether the PFO is a culprit or a bystander. Arguably, the battle lines are between cardiologists and neurologists. The former have championed transcatheter PFO closure with a litany of ingenious devices; the latter have insisted that closure is unnecessary and that anticoagulation (usually with warfarin) is proper therapy. The published studies in the last 15 years have been peppered with reports supporting either side and have generated some vexing questions along the way. For example, in the report by Mas et al. (1), why is the association of an atrial septal aneurysm (ASA) with a PFO associated with stroke, but a PFO alone is not? Does the to

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and fro motion of the ASA set up currents of blood flow favoring right-to-left shunting or does thrombus form on the ASA? Why does age seem to be a factor? Are there truly more bits of thromboembolic debris floating through the right side of the circulation as we age, thereby increasing the risk of a particle being shunted right to left during a Valsalva maneuver? In the PICSS (Patent Foramen Ovale In Cryptogenic Stroke Study) trial (2), a substudy of the WARSS (Warfarin–Aspirin Recurrent Stroke Study) trial, the presence or absence of a PFO is equally associated with stroke.

On the other hand, closure of the PFO is supported by reports from numerous cardiac centers interested in transcatheter therapies. None are randomized trials, but the registries seem to show that the incidence of recurrent cerebral events is decreased. The 1 question that those registries do not answer is: Why, if the PFO was indeed the culprit, do *any* recurrent events occur? Is incomplete closure and residual shunting the cause of recurrence, are there overlooked sources of thromboembolism on the left side, are the devices themselves a source of left-sided thrombus, or is something else going on?

Protagonists for both sides have long supported the concept of a randomized trial of closure versus anticoagulant therapy. Multiple trials were begun, and failed for lack of adequate enrollment, but now 1 trial, the CLOSURE (Evaluation of the STARFlex Septal Closure System in Patients With a Stroke or TIA Due to the Possible Passage of a Clot of Unknown Origin Through a Patent Foramen Ovale [PFO]) trial (3), using the STARFlex device (NMT Medical, Boston, Massachusetts) has been fully enrolled and the outcomes will be available in about 1.5 years. All of us look forward to seeing those data.

But hold on. In this issue of *JACC: Cardiovascular Interventions*, Rigatelli et al. (5) show data that shed a completely different light on the possible mechanism of cryptogenic stroke in the presence of a PFO, especially if a large ASA is also present. They postulated that in patients with PFO and ASA, there is left atrial (LA) dysfunction simulating atrial fibrillation–like physiology, Studying almost 100 patients with previous stroke referred for transcatheter PFO closure, they found that before closure, the subjects had significantly greater reservoir function, reduced conduit function, and LA ejection fraction. Furthermore, two-thirds of the PFO patients also had moderate-to-large ASA, and of the patients with both PFO and ASA, spontaneous echo contrast was seen in about one-half. None of the patients with PFO alone had spontaneous echo contrast. These findings were similar to a group of patients that had atrial fibrillation! Not only that, but patients with PFO and ASA had worse functional parameters, a higher percentage of left-to-right shunting, and more coagulation abnormalities than those with PFO alone, which might account for the increased number of cerebral events seen in those patients pre-closure.

These are intriguing data, but any report has potential flaws, and this report is no exception. The authors do not tell us what definition of ASA was used. It is not totally clear if all parameters were measured as recommended (4), and the article does not report LA volume index. Whether these are important considerations will await larger patient numbers and substantiation of the concept by other investigators. Further, the report indicates a surprisingly high percentage of patients with abnormalities of the coagulation cascade and patients that exhibited a "smoke-like phenomenon" by at least 1 imaging tool. The picture of "smoke" in the curl of the ASA seen by intracardiac echo and published in the article is undeniable. However, most interventional cardiologists and their echocardiographic colleagues have seen only rare patients exhibiting that phenomenon in their series of patients being evaluated for PFO closure. Do these data reflect some kind of selection bias?

To the authors' credit, they restudied their patients after closure. Active and passive emptying of the left atrium as well as conduit function and LA ejection fraction moved toward normal levels of healthy control subjects. Three

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closure devices were used in their patients according to anatomic features of the atrial septum, but it is difficult to reach any conclusions about efficacy of one over the other due to the different anatomic baselines.

The report (5) makes provocative reading because it points out that the PFO may not have as large a role as we think in the cryptogenic stroke scenario. But for patients with PFO associated with ASA, the data of Rigatelli et al. (5) point out the increased potential of right-to-left shunting. The report indicates that the Mas et al. (1) report and the PICSS report, which seem possibly contradictory, may both be correct. More importantly, their data show that LA function is clearly altered in the presence of a PFO and ASA and is similar to that of patients with atrial fibrillation, which might predispose them to a cardiac source of thromboembolism. It should be comforting to cardiologists that the authors of this article contend that transcatheter PFO closure returns LA function toward normal, which presumably diminishes the risk of LA thrombus. But the devices used by the authors are large closure devices and influence the ASA as well as close the PFO. Maybe size (or also flexibility) of the closure device is also important in restoring LA function. Not all closure devices may have the same effect on restoring LA function, especially small, suturelike devices, and would therefore allow continued LA predisposition to clot. That might help explain some of the recurrent event rate after transcatheter closure reported in the registries. The LA function might not have been restored toward normal in all patients. Take that thought a step further. Suppose the CLOSURE trial shows no benefit of PFO closure. That outcome might then be explained by the device's possible lack of effect on the ASA and on restoration of LA function (closure is necessary, but not enough). Now that raises some interesting questions.

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