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EDITORIAL COMMENT

A Positive Bubble Test Post–Patent Foramen Ovale Closure

Was Satisfaction-of-Search to Blame?*

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Verification of successful patent foramen ovale (PFO) closure is standard practice and typically involves echocardiographic or transcranial Doppler studies after the placement of a medical device that acts like a paperclip to hold the septum primum and secundum together. The small bubbles injected into a systemic vein typically do not transit through the pulmonary circulation, such that when bubbles are visualized on the left side of the heart or detected by transcranial Doppler, the question becomes why. Was the procedure ineffective, or is there another reason for right-to-left shunting (RLS)?

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In this issue of *JACC: Cardiovascular Interventions*, the study by Shah et al. (1) provides valuable insights into this important issue, especially in the current era of a renaissance in the use of PFO closure to reduce the risk for recurrent ischemic stroke from presumed paradoxical embolism (2). This study was based on their clinical experience over 17 years involving 568 patients receiving the Amplatzer PFO Occluder. The investigators show that: 1) residual RLS decreased over time; 2) some patients with residual shunts had an additional type of cardiovascular lesion enabling RLS that then could be treated; 3) a small fraction of those with residual RLS had persistent flow through the PFO device; and 4) eventually, at 2 years post-procedure, only 2.8% had persistent RLS that was believed to be both minimal and without clear cause. The investigators also include an excellent discussion that provides a review of bubble size and normal pulmonary artery-vein connections that are not malformations.

A potential issue related to this study is the well-known phenomenon of satisfaction of search (SOS) (3). Medical imaging is often ordered with a specific goal in mind, such as finding a source of RLS. Once a potential cause is found (i.e., a PFO is identified), the person performing the examination as well as the person interpreting it may look for other causes with less vigor or not at all. Perhaps cardiologists need to be aware of SOS more than radiologists, because a cardiologist is often the clinician ordering and interpreting the test. This could bias against spending the additional time and effort to perform a complete imaging examination and interpretation.

What are other take-home points from this study that clinicians should consider in their practices?

First, be aware that other causes of RLS can coexist in many patients who have PFOs, and do not commit the image interpretation error of SOS. These other causes may be intracardiac or extracardiac. During the initial patient evaluation, it is reasonable to ask questions and perform a physical examination that may suggest the presence of hereditary hemorrhagic telangiectasia. This is the most common cause of pulmonary arteriovenous malformations in adults. Because 25% of the general population have PFOs, it would be expected that a similar percentage of people with pulmonary arteriovenous malformations have PFOs that could be incidental rather than pathogenic for paradoxical embolism.

Second, the frequency of finding other causes of paradoxical embolism is likely to be lower if there is no initial transesophageal echocardiography, if it is performed without careful attention to other

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potential causes of RLS, and if the SOS error is made. Furthermore, failure to detect an alternative cause of RLS will be substantially higher if there is both a lack of an excellent transesophageal echocardiographic study pre-procedure and if the "minimalist" approach to PFO closure is used that incorporates only fluoroscopic imaging and no ultrasound guidance.

Third, the leading cause of persistent RLS is incomplete closure of the PFO. This study showed a steady decline in the incidence of persistent RLS from 19.5% at 4 months, to 8.4% at 11 months, and to 2.8% at 24 months. What is the mechanism of this slow reduction in post-procedural RLS that is not related to finding and closing other causes of RLS?

The mechanical effect of the device holding the septum primum and secundum together is immediate, but in many patients the mechanical effect can be slightly overcome with a Valsalva maneuver that transiently reverses the right/left atrial pressure gradient and allows the thin septum primum to move enough between the 2 discs to allow some bubbles to pass into the left atrium.

The slow and poorly understood process of device "healing," often referred to as neoendothelialization, appears to complete the closure process in the majority of patients. Medical imaging of all forms cannot visualize this process on many types of implanted devices, because it is a layer that is often only a few cells thick. Our understanding of neoendothelialization, albeit incomplete, comes from the rare cases when devices were inspected at the time of autopsy or open heart surgery. These devices often had incomplete tissue covering the large surface of the device, filling the crevices at the edge of the discs, and bridging the gap between the device edge and the adjacent tissue (4–7). More in-depth studies of PFO, atrial septal defect, and left atrial appendage closure device healing have documented the time-dependent process of immediate fibrin deposition, an inflammatory reaction, fibroblast-like cells, and then pseudo-intima with an organized cellular arrangement with superficial cells being endothelial cells (8,9). This process is important for the closure process and the reduction in the likelihood of thromboembolic and infectious processes occurring on exposed device components. Little is known regarding structural heart disease devices and patient factors that promote or retard device neoendothelialization.

Fourth, after PFO closure, the timing and need for repeat echocardiographic studies are somewhat arbitrary, but there are some reasonable considerations to follow.

Once complete closure after PFO closure is clearly documented from a well-conducted transthoracic echocardiographic study with provocative maneuvers, there is no need to routinely continue to perform follow-up studies. This was not a finding of the present study but is reasonable from a cost-effectiveness perspective.

If there is residual RLS, a follow-up study is needed. Small residual RLS, especially if occurring only with the Valsalva maneuver, suggests that more time needs to be allowed for closure to occur. If the amount of RLS is quite trivial (i.e., 1 or 2 bubbles), it may not warrant further studies. The PFO trials have been reassuring in not showing an association between residual RLS and recurrent ischemic stroke.

Large residual RLS should prompt reexamination of pre-procedural and intraprocedural imaging studies to see if something was missed or if the device fit the anatomy poorly. Subsequently, transesophageal echocardiography should be performed that allows examination of the device, visualization of residual flow location by color flow Doppler and bubbles, examination of the entire atrial septum, and observation of each of the pulmonary veins during bubble injection, because pulmonary arteriovenous malformations are often first suspected during this specific effort.

Recurrent clinical events should prompt immediate transesophageal echocardiography to assess the location of residual RLS in addition to detection of other potential rare causes of the clinical event, such as thrombus on the device.

It should be rare to miss other enabling anatomic abnormalities for paradoxical embolism with a complete pre-procedural evaluation. A performance metric for centers performing PFO closure could be the incidence of residual RLS due to other causes. This metric requires follow-up of all patients, and it may be difficult because many may be seen post-procedurally by other clinicians and at other facilities. Hopefully with more integrated health care systems and well-designed electronic medical records, the long-term outcomes of the interventions we perform can be completely and comprehensively tracked.

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