The Gestalt Approach to PFO and Cryptogenic Stroke

Laura Gerik, MS

HOUSTON METHODIST DEBAKEY HEART & VASCULAR CENTER, HOUSTON, TEXAS

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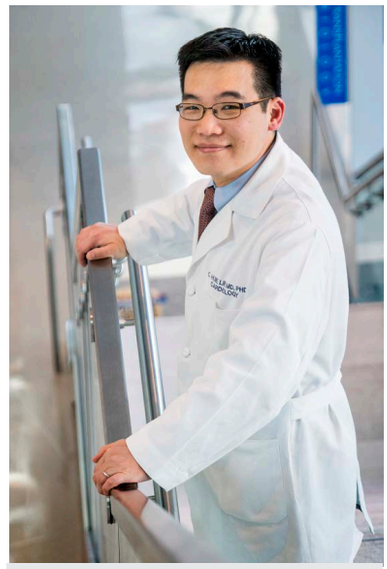
The latest clinical trials testing patent foramen ovale (PFO) closure for cryptogenic (unknown-origin) stroke offer promising results; just last month, the New England Journal of Medicine published the results of two new research trials and long-term follow-up of an earlier trial that all demonstrated significant reduction in recurrent cryptogenic stroke risk for PFO patients treated with closure. However, the American Heart Association/American Stroke Association's (AHA/ASA) most recent guidelines explicitly recommend against PFO closure for stroke. So what is a cardiologist to do? In a world where indications for PFO closure are evolving so rapidly that trial results and official guidelines seem contradictory, there are no blanket recommendations. Thus, according to C. Huie Lin, M.D., interventional cardiologist at Houston Methodist Hospital, deciding who needs PFO closure depends as much on the "art of medicine" as science.

Consider this whirlwind history: In the early 2000s, PFO closure was available to close PFOs in cryptogenic stroke patients through an FDA humanitarian device exemption, which was revoked for overuse in 2006.1 In 2014, following a clinical trial with that failed to show statistically significant benefits to PFO closure in stroke patients, the AHA/ASA issued a class 3 recommendation against PFO closure for stroke. (However, Lin points out, they were careful to specify that "there's no data to support" PFO closure, not that closure would cause harm.) Then a quick succession of clinical trials indicated that PFO closure actually did help prevent recurrent cryptogenic stroke (the RESPECT trial showed a 45% reduction in risk of recurrence compared to medical therapy alone2). Thus, in 2016—a decade after pulling the device off the market—the FDA approved the treatment again, this time without the humanitarian restriction.3 As of October 2017, the Amplatzer PFO Occluder (St. Jude Medical) is the only FDA-approved device for this indication, although devices such as the Gore Cardioform and Gore Helex Septal Occluders are being used in clinical trials. For now, official guidelines have yet to be updated, and the science of when to treat PFO is far from settled.



C. Huie Lin, M.D., Ph.D.

Lin and colleague John Neill, M.D., recently published a review of PFO closure for cryptogenic stroke in the *Methodist DeBakey Cardiovascular Journal.* PFO is an artifact of fetal development found in 25% to 30% of adults. In most people, this hole between the heart's left and right atria closes after birth. However, in some the hole does not seal completely, and some degree of PFO remains. Although most adults never experience a problem with their PFO—and many never even know it's there—the condition is suspected to play a role in some cryptogenic strokes.

Cryptogenic strokes—those without an apparent vascular or arrhythmic origin—account for about a quarter of reported strokes. PFO emerged as a suspect when researchers observed that up to half of patients with cryptogenic strokes had a PFO, a surprisingly high prevalence compared to the population. Moreover, thrombi have been observed in the PFO itself, and it is speculated that these clots could pass into the right atrium and into systemic circulation to cause stroke.

Right now, the debate is less about whether PFO *can* cause stroke and more about *which* PFOs cause stroke and who needs to be treated. "We think the AHA/ASA guidelines will change. I think there's a pretty strong need for it and I think there are a lot of people who can benefit from PFO closure. But we're still somewhat circumspect because one-third of the population has PFO, and clearly one-third of the population does not need their PFO closed," Lin says.

One of the biggest problems, as Lin sees it, is current noninvasive imaging modalities. “We really can’t assess how large a PFO is by noninvasive studies,” he explains. “Sometimes when you look at an echocardiogram, the PFO may not look very large and the bubble study [a way to assess for PFO or shunt by injecting agitated saline and looking for bubbles appearing in the right atrium] may not be very significant. But then when we do the device closure by putting a wire across the PFO and propping it open, we may see a very large hole.” Lin wonders whether size is truly one of the keys to this “100-million-dollar question: Which PFOs really need to be closed and which ones don’t.”

Other than sizing, Lin hopes to see more research into the characteristics that predispose different patients with PFO to stroke. “I think the really important thing is to risk stratify which PFO closures have to happen. Is there a certain population that we need to be closing? Are there certain characteristics about their hearts? Are they people of certain ages? Are there anatomical characteristics of the PFO that indicate higher risk and therefore they should be closed?” he says. “I really want to be careful about putting too many devices into too many patients. That makes me nervous. Especially because these are young patients and they are going to have a lifetime exposure to this device.”

Without these answers, interventional cardiologists evaluate patients using tools such as the Risk of Paradoxical Embolism (RoPE) score—which assigns a patient “points” based on lack of traditional stroke risk factors such as hypertension or smoking—and a fair bit of, as Lin says, *gestalt*.

“Ultimately we have to think about what’s going to happen to the individual patient. So even though we think that someone will have the most bang for their buck if they’re less than 60 years of age, we have made a few exceptions because obviously 60 is not the same for everybody,” Lin explains. “We may have a 62-year-old or a 70-year-old who looks like they’re in their 40s. I have a patient like that who works out more than I do and has no vascular risk factors whatsoever, and we think probably he should be treated for PFO closure because there’s really no other reason for him to have a stroke. Whereas we could potentially have a 40-year-old who has multiple areas of atherosclerotic disease who we think is not a great candidate for PFO closure because they have every reason in the world to have a stroke besides PFO. I think we have to weigh every individual carefully and take it on a case-by-case basis. This is kind of the art of medicine that guidelines and clinical trials don’t necessarily answer for us.”

For Lin, the decision often comes down to the cause of his patient’s strokes—or, more specifically, whether his team cannot identify any cause other than a PFO. It’s less a definitive diagnosis than a process of elimination. One of the complicating factors is the relative youth of his patients, who are usually in their 20s to 40s. Fortunately, many of them recover from their strokes with minimal residual problems. The downside is that, short of tracking a stroke on an MRI, it becomes difficult to objectively prove that a stroke occurred, which is key to deciding to proceed with treatment.

Someday, Lin hopes to not only be able to determine which PFOs warrant closure after a stroke, but ultimately to predict who needs the intervention to prevent a stroke in the first place. Although Lin admits that “we’re nowhere near to sorting out” the latter, risk stratification for PFO patients after a first stroke seems nearer on the horizon.

Until then, early intervention and multidisciplinary evaluation is key. “If there’s concern for cryptogenic stroke, then it’s always worthwhile identifying a stroke neurologist who can see and identify etiologies and then from there refer to an interventional cardiologist who has the practice and skills to close a PFO,” Lin says. “I think it’s very important that a comprehensive multidisciplinary evaluation be done for all these patients.”

Corresponding Author:
lgerik@houstonmethodist.org

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