Patent foramen ovale (PFO) is not uncommon—it appears in perhaps 10% to 25% of the population—but only a small percent of cases will produce any clinical sequelae, such as refractory hypoxia, orthodeoxia-platypnea syndrome, or migraine headaches. PFO is most notorious, however, for its association with paradoxical embolus and cryptogenic stroke (1). Conclusive proof of a causal relationship between PFO and the clinical embolic presentation remains elusive, as it is rare to visualize a paradoxical embolus in real time. More perplexingly, trials aimed at closing PFOs with various innovative devices have failed to significantly reduce clinical events, which indicates that there may be a multitude of underlying pathogenetic factors (2,3). Nevertheless, accurate and, preferably, noninvasive diagnosis is needed to evaluate future stroke risk and help determine therapeutic decisions.

Diagnosing a PFO: Is There a Gold Standard?

PFO diagnosis has certainly evolved from the days when a catheter had to cross the interatrial septum (sometimes inadvertently) during heart catheterization. We can now detect a transient right-to-left shunt (RLS) with contrast transthoracic echocardiography (TTE) or use transesophageal echocardiography (TEE) to visualize a PFO and the site of the shunt simultaneously. Transcranial Doppler (TCD) uses the same principle of ultrasound microbubble detection of an RLS by demonstrating changes in Doppler signal from the microbubbles in the middle cerebral artery vessel(s). Each of these 3 ultrasound modalities has advantages and limitations in the workup of a patient with stroke, but they should, in principle, be equivalent: they all detect RLS by microbubbles, either visually (TTE and TEE) or by Doppler shift (TCD). Therefore, provided that the techniques and visualization are adequate, and the physiology behind the presence of the shunt (at rest or with a provocative maneuver) is similar, there should be no significant difference in diagnostic accuracy. Rarely, however, are these tests performed simultaneously for a true comparative accuracy of detection of RLS.

In this issue of *JACC*, however, Mojadidi et al. (4) report on a bivariate meta-analysis of prospective studies comparing PFO detection with TCD to the standard of TEE. The investigators performed an exhaustive search, identifying 27 reports with a total of 1,968 patients. Agitated saline was used as the contrast agent in the majority of studies (41%), and the Valsalva maneuver was used as the sole provocative method in 86%, with cough in another 10%. There was some variability among studies in the definition of an RLS (from 1 to 15 bubbles by TCD and from 1 to 20 bubbles by TEE). The sensitivity of TCD for the diagnosis of intracardiac left-to-right shunt was 97%, with specificity of 93%; as expected, an increase in specificity was seen when the number of bubbles detected by TCD was increased from 1 to 10.

Although there may be small differences between the 2 techniques in detecting an RLS, they are, for all intents and purposes, equivalent in revealing PFO. The lower specificity seen with

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TCD could be related to the choice of the standard for comparison, which raises the question, what is the gold standard for diagnosing a PFO?

The diagnosis of a PFO, from the perspective of clinical significance, requires both an anatomic and a physiologic aspect. The physiologic assessment of an RLS is usually performed using contrast TTE or TCD before an anatomic confirmation is demonstrated, usually by TEE. This poses a challenge, because for the shunt to occur, right atrial pressure must exceed left atrial pressure at least transiently (5,6). This may happen at rest but more often after provocation with a Valsalva maneuver (with or without cough). Because these provocation techniques require physical effort, coordination, and adequate timing, there is inevitable variability in the results and detection of RLS. A previous study documented that forced breathing into a tube with monitoring of generated pressure produces higher and more reliable pressure than that generated with Valsalva and thus leads to higher RLS detection rates (7). This would be relevant to the standard of TEE in the present study, as patients are usually sedated and instrumented with a transesophageal probe, rendering the effort generated by a Valsalva maneuver less than optimal compared with the awake baseline state. Thus, although TEE is excellent in delineating the interatrial septum and identifying a PFO anatomically, it may not be the true gold standard for detecting RLS and is a source of “false-negative” contrast studies. For this reason, and provided that visualization of the chambers, imaging window, and technique are adequate, TTE with contrast injection at rest and upon repeated Valsalva is a more robust standard for the detection of an RLS than TEE. Because TCD is performed in a setting similar to TTE, provocation maneuvers are more reliable, and thus detection of RLS is more robust. The accuracy of TCD is also, of course, dependent on good technique, as artifacts can simulate Doppler signals.

Only with a very small shunt (about 1 to 3 bubbles) is there possibly a difference in sensitivity between echocardiographic and TCD techniques: such few bubbles can be missed in a tomographic echocardiographic plane and will be more readily detected using a volumetric Doppler approach (TCD). However, if the bubbles are indeed very few, they may not go through the middle cerebral artery from the left cardiac chambers. Regardless, when dealing with such a small shunt size, its clinical significance starts to become questionable.

Toward Optimal Test Utilization

Recently, the clinical indications and practice guidelines for TCD were published by the American Society of Neuroimaging, among which are screening for RLS, determination of cerebral blood flow, and evaluation of embolic events during surgery or interventions on the aorta or cerebral vessels (8). Although TCD is a fine, noninvasive technique to determine whether an intracardiac shunt is present, it is not particularly good for differentiating an intracardiac shunt from a pulmonary arteriovenous fistula, and it does not provide the anatomy of the shunt or other possible sources of embolism that may need to be investigated (4). The older the patient, the higher the likelihood of other potential cardiac sources of emboli, such as left atrial or ventricular thrombi, valvular disease, or disease of the thoracic aorta.

The question that arises then is, what are the next steps after the TCD test? Do negative results obviate the need for TTE or TEE? How about the converse scenario: what is the next step after positive results on TCD? Should it be TEE or TTE followed by TEE? There are no simple answers to these questions, as the data have not been collected, but they are important to consider, as these approaches would require patients to undergo several tests (scheduling, inconvenience, intravenous lines, and so on) with overlapping, redundant diagnostic power and additional cost.

In short, in the evaluation of patients with possible embolic stroke, the cardiac workup does not stop with TCD, whether or not it reveals RLS. In patients with RLS documented by either TTE or TCD who have had clinical events, usually TEE is subsequently performed, particularly when results would alter management. These include verification that the underlying condition of the shunt is a PFO (particularly if occlusion of the defect is contemplated); assessment of other causes of RLS, such as an atrial septal defect, fenestrations of the interatrial septum, or a pulmonary arteriovenous fistula; documentation of a PFO (with or without an interatrial septal aneurysm) in the case of a technically difficult transthoracic examination; and evaluation of other potential sources of emboli (9).

Clinically, it is my experience that negative results on TCD for RLS do not dissuade clinicians from ordering TTE (or TEE) to look for other cardiac sources of emboli beyond a PFO, nor do positive results on TCD preclude further evaluation with echocardiography. Of interest is that the relative value unit per the Centers for Medicare
and Medicaid Services for 2014 is identical for TTE with contrast and TCD, at 1.30, whereas that for TEE is 2.65. Further studies are needed to delineate the best approach to using these techniques for optimal diagnosis and management of patients with suspected cardiac emboli in a healthcare system in which both cost and patient outcomes are important. Further research is also needed to determine whether there are high-risk groups that could be identified—on the basis of the magnitude of the shunt, the need for provocation, the size of the defect, and other clinical criteria—and that would clearly benefit from interventions.

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