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Diagnosis of an Anatomically and Physiologically Significant Patent Foramen Ovale

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The presence of an anatomically and physiologically significant patent foramen ovale (PFO) appears to be associated with several different clinical conditions,[1] including unexplained neurological decompression sickness (DCS) in divers[2–7] and aviators/astronauts,[8–9] cryptogenic stroke,[10–15] and the platypnea-orthodeoxia syndrome.[16–20] Recently, it appears that migraine headache also may be associated with a PFO.[21–25]

Definition

A PFO is a common anatomical finding in the general population, with an autopsy incidence of 27–29%.[26,27] It is a remnant of the fetal circulation, as oxygenated placental blood enters the right atrium (RA) via the inferior vena cava (IVC), and then crosses the valve of the foramen ovale to enter the systemic arterial system.[28] IVC flow is preferentially directed toward the interatrial septum and the foramen ovale. Superior vena cava (SVC) flow is directed away from the interatrial septum by the crista interveniens. In addition, coronary sinus flow is directed away from the interatrial septum.[29] After birth, the flap of the foramen ovale (septum primum) will close against the atrial septum (septum secundum), usually occurring within the first 2 years. Incomplete fusion results in an oblique slit-like valve, termed a PFO. Why fusion is incomplete in these individuals is not known, but one study found that siblings of women with a PFO were more likely to have a PFO than siblings of women without a PFO.[30]

PFOs vary in anatomical size and physiological function. In a patient presenting to the echocardiography laboratory with one of the aforementioned clinical diagnoses, characterization of a PFO anatomically and physiologically is important. This anatomical and physiologic assessment may help the clinician decide if a PFO likely is associated with the presenting diagnosis, or is an incidental clinically insignificant finding.[1]

Before the advent of echocardiography, diagnosis of right-to-left shunts was problematic, as generally there is no typical abnormality on physical examination, electrocardiogram or chest x-ray. Unless a right heart catheter or pacemaker wire inadvertently crosses into the LA, these techniques are not suitable for PFO diagnosis. Generally, methods such as oximetry or indocyanine green curves are not useful for PFO detection, as the amount of shunting is below a threshold level of detection using these techniques. [31–33]

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Echocardiography for PFO Detection

Echocardiography has emerged as the principle method for diagnosis and assessment of PFO, particularly the modalities transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE).[1] TTE is used initially with saline contrast for detection of a right-to-left shunt. Using bacteriostatic saline containing benzyl alcohol as a preservative keeps agitated bubbles in solution longer, and appears to be better than that from an intravenous saline bag.[34] TTE imaging for contrast injections is performed from an apical four-chamber view, as parasternal windows will cause contrast filling the right heart to impair visualization of the LA and left ventricle (LV).

Consistent with shunting at the atrial level is saline contrast appearing in the left heart within three cardiac cycles of its appearance within the right heart. If contrast appears within the left heart only after greater than three cycles, it most likely has traversed the pulmonary circulation and arrived within the left heart via a pulmonary arteriovenous (AV) fistula.[1,34]

Several studies suggest a higher detection rate for right-to-left shunting when saline contrast injections are performed via a lower extremity vein, as compared to the right antecubital vein.[35,36] This finding may very well be reflective of IVC and SVC flow patterns entering the RA in utero.[28,29]

If saline contrast is noted in the left heart by TTE, or if by TEE color flow Doppler or contrast is noted to flow right to left during normal respirations, this is termed a resting PFO.[1] When a resting PFO is detected, this often represents a physiologically significant PFO, and is associated with DCS,[2–7] cryptogenic stroke,[10–14,37], and platypnea-orthodeoxia.[19,20] By TTE and TEE, the Valsalva maneuver (and also repetitive cough) may enhance atrial level shunting,[1,38] because of an increase in right heart pressures.[39] However, it appears that a resting PFO may have a higher risk of a clinical event, than that of a PFO that shunts only during a provocative maneuver.[1,37]

TEE versus TTE

For both antecubital and femoral routes of saline injection, TTE detection of a right-to-left shunt is lower than TEE, which appears to be the present-day reference standard for PFO diagnosis. TEE allows for direct visualization of the interatrial septum and also saline contrast shunting through a PFO. Recently, however, TTE using native tissue harmonics has had an improved sensitivity and specificity (compared to TTE with fundamental imaging), using TEE as the reference standard.[40,41] In addition, it appears that the Valsalva maneuver and cough are performed with a better effort compared to TEE, notably because of the esophageal probe position and sedation for the TEE intubation procedure.[34] Doppler of mitral inflow using peripherally injected agitated saline appears almost as sensitive as TEE for PFO detection.[42] An automated scoring system using this method correlated with PFO size as measured by TEE.

It is felt by several investigators that a high quality TTE (using native tissue harmonics) with saline contrast should exclude a PFO with a predictive value similar to that of TEE.[34,41] However, TTE studies that are less than excellent in quality should proceed to TEE to "rule out" a PFO. In addition, if a PFO (atrial level right-to-left shunt) is detected by TTE, a TEE should be performed to further evaluate the atrial septum.

PFO Quantification and Clinical Application

Measurement of PFO anatomical size by direct measurement of the slit-like defect width is often possible.[1,42,43] When using color Doppler to aid in measurement of slit-width, the measurement may slightly overestimate size, as compared to autopsy correlation.[44]

Determination of both anatomical size and functional significance of a PFO have been performed mostly in evaluation of patients with cryptogenic stroke, with the source presumptively paradoxical embolism through the PFO.[45–47] Reports in the literature document thrombi "wedged" within a PFO in patients presenting with stroke.[1,48,49] In addition, other findings often noted in patients with cryptogenic stroke implicating a PFO as the potential source include the following:

1. The cerebral infarct territory usually suggests an embolic source.[50,51]
2. Anatomically larger sized PFOs and also resting PFOs are more frequently noted in patients with cryptogenic stroke than controls.[1,51–55]

3. There appears to be a significant incidence of deep venous thrombosis (6% to 27%), pelvic thrombus (20%), and calf vein thrombus in patients with cryptogenic stroke.[56–60]

Detection of saline contrast (normal respiration and Valsalva maneuver) within the left heart has been used as criteria for grading the right-to-left shunt through a PFO.[43,45–47] These reports, however, use various amounts of LA saline contrast as criteria for grading PFO functional significance. In general, the larger the PFO anatomically measured (normal respirations and Valsalva maneuver) and the larger the number of "bubbles" counted in the LA in a single "frozen frame" (normal respirations and Valsalva maneuver) the more likely a patient was to have multiple neurological lesions detected by MRI or CT of the brain. Generally, a "small shunt" would have <5 bubbles noted in the LA in a single frame, a "moderate shunt" as 5–25 bubbles, and a "large shunt" as >25 bubbles.[1,34]

Associated Anatomical Structures

As part of the PFO evaluation in the echocardiography laboratory, one should look for associated anatomical structures, namely that of an atrial septal aneurysm (ASA)[61–66] and the Chiari network.[67] An ASA is defined as a total septal excursion of 15 mm or more.[65,68] Its incidence by autopsy study is 1%,[69] and 0.22% by TTE.[70] In patients with cryptogenic stroke, an ASA appears to be more prevalent than in control subjects (15% vs 4%).[65] When an ASA is detected in the general population, it is associated with a PFO in about 70%. In addition, patients having an ASA with PFO tend to have larger PFOs both anatomically and physiologically.[1] This association appears to be important when evaluating a PFO for significance in a patient presenting with cryptogenic stroke.[71]

The Chiari network are fibers originating from either the Eustachian or Thebesian valve, and are attached to the upper wall of the RA or the interatrial septum. These fibers result from incomplete resorption of the septum spurium and the right valve of the sinus venosus.[72] The autopsy incidence of the Chiari network is reported as 2–3%.[73] A prominent Eustachian valve may be mobile and fenestrated, but it does not attach to the upper wall of the RA or to the interatrial septum. This, by definition, should not be termed a Chiari network. The TEE incidence of the Chiari network is 2% (TTE <1%). A PFO was detected in 83% of patients with the Chiari network, and the right-to-left shunt was noted to be more "intense." In addition, a coexistent ASA was found in ~20% of patients.[67] It appears that an ASA and the Chiari network are found together more frequently than in the general population, and when a PFO coexists (70% of patients with ASA have PFO), these patients appear to have a larger PFO both anatomically and physiologically.

Although TEE is considered the reference standard for detection of PFO, both false-positive and false-negative studies may occur. As discussed earlier, there is a lower saline contrast detection rate by injection of contrast via the antecubital vein as opposed to the femoral venous route. This is due to IVC directed flow toward the interatrial septum, and SVC flow directed laterally. Other false-negative TEE results may occur from inadequate imaging within the esophagus, an improper Valsalva maneuver, or elevated LA pressures, thus preventing right-to-left shunting of saline contrast.[74,75] A false-positive contrast study may occur with a shunt through the atrial septum other than a PFO. Most often, this is a secundum atrial septal defect.[76] A pulmonary arteriovenous fistula will allow saline contrast to enter the LA from the right heart, but usually contrast will appear within the LA with a delayed appearance (usually >3 cardiac cycles). In addition, so-called "debris" may be seen to enter the LA from the pulmonary veins, especially after release of the Valsalva maneuver.[77,78]

In summary, a few concluding comments include:

1. PFO is common in the general population.
2. Not all PFOs are the same. Anatomical size and physiology varies from patient to patient.
3. PFO anatomical size and physiological functional "size" are not necessarily correlated.
4. Several clinical diagnoses appear to be associated with anatomically and physiologically significant PFOs, including DCS (divers, high-altitude pilots, and astronauts), cryptogenic stroke, platypnea-orthodeoxia, and migraine headache.
5. An ASA and the Chiari network are associated with each other and with larger PFOs
6. TEE is presently the reference standard for diagnosis of PFO along with its anatomical and physiologic significance.

7. Methodology in TEE evaluation for PFO is important.
8. Although TEE is presently the reference standard for PFO diagnosis, both false-positive, and false-negative results may occur.
9. Several studies of patients with cryptogenic stroke and DCS have correlated an increased prevalence of PFO and PFO "size."
10. Characterization of PFO functional "size" has varied from study to study, with different criteria used for severity grading of a shunt.
11. In the proper clinical context, a "resting" PFO detected by TTE may be clinically significant.

PFO is implicated in several clinical diagnoses in patients presenting to the echocardiography laboratory. It appears that the size of a detected PFO should be evaluated, as the risk for atrial level transit of emboli appears to be greater with larger lesions. In addition, the echocardiographer should evaluate for an ASA and a Chiari network, because of the association with a significant PFO.

Patients with a PFO can be categorized according to several characteristics (large/small PFO, normal respiration/Valsalva-induced shunting, associated anatomical structures). Which methodology for evaluation of a PFO's features that are clinically important in assessment of an associated diagnosis is not certain. The question remains as to which PFO is significant for a given clinical diagnosis.

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