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The diagnosis and treatment of paradoxical embolism: a systematic review

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ABSTRACT

One in five adults has patent foramen ovale (PFO), which is typically without symptoms. Because of the low pressure in both atria and the anatomical position of the septum secundum, there is no left-to-right shunting and little right-to-left shunting in the general condition; however, when the right atrial pressure increases, this slit-like flap separates and allows right-to-left shunting. According to the Johnson criteria, simultaneous occurrences of arterial emboli, such as those caused by cerebrovascular accident or pulmonary embolism, demonstrate the presence of paradoxical embolism through a PFO. When a patient presents with multivascular arterial embolism, the clinician should perform a contrast transthoracic echo, a transesophageal (TEE), a real-time three-dimensional TEE, and even an intracardiac echocardiography (ICE) in order to differentiate between PFO, flat atrial septal defect (ASD) and hybrid defects. The randomized trials that have assessed therapeutic interventions for paradoxical embolism have not produced any clear guidelines as to how best to treat this condition. The classic treatment is surgical embolectomy with exploration of the right chambers and the pulmonary arteries under full cardiopulmonary bypass. Patients with a history of ≥1 paradoxical embolism may be indicated for device PFO closure.

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Introduction

According to the Johnson criteria, simultaneous occurrences of cerebrovascular accident and pulmonary embolism indicate the presence of paradoxical embolism, as follows:

"1. A source in the venous circulation for embolic material

2. A Communication between pulmonary and systemic circulation

3. Right-to-left shunting, in transient or long-standing" (1).

In 25-30 percent of individuals who present with paradoxical embolism, a patent foramen ovale (PFO) can be detected (2). The interatrial septum has two parts: the septum primum and the secundum. The septum primum forms from the top of the atrium downward and the septum secondum develops from the bottom of the atrium upward and to the right of the septum primum. There is a slit-like opening between the two parts of the interatrial septum that is called a PFO. Because of low pressure in both atria and the anatomical position of the septum secundum, no left-to-right shunting and little shunting is observed in general cases of paradoxical embolism; however, when the right atrial pressure increases during physiological conditions, such as straining, the Valsalva maneuver, or coughing, this slit-like flap separates and allows right-to-left shunting. Furthermore, this type of shunting may

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become more marked in cases where the right atrial (RA) pressure increases due to pathology such as pulmonary embolism. There is also a so-called "flow phenomenon" that describes a preferential blood flow from the inferior vena cava towards the atrial septum as a part of the fetal circulation.

Some cases have reported the coexistence of paradoxical emboli with pulmonary (PE) systemic embolism and deep vein thrombosis (DVT), especially in patients with the "hybrid defect," which is defined as fenestrated secundum atrial septal defect with septal aneurysm (3). Less than 2% of all cases of systemic arterial emboli are paradoxical (4). As high as one in five of the general population has a PFO (5), which is the most common cardiac defect in association with paradoxical embolism.

When a patient presents with multivascular arterial embolism, it is essential that a transesophageal (TEE) and even a intracardiac echocardiography (ICE) is performed in addition to the transthoracic echo (TTE) to differentiate between PFO, flat atrial septal defect (ASD), and hybrid defects. TTE cannot differentiate between PFO and ASD, and is not suitable for guiding device closure of PFO; however, with contrast echo (agitated saline injection) during the Valsalva maneuver at the time of contrast injection, a right-to-left shunt can be diagnosed. If contrast bubbles appear in the right atrium, the patient should be asked to immediately stop straining. If the bubble passes through fossa ovalis during the first three cardiac cycles after release from the Valsalva maneuver, the contrast study is positive and precise echocardiography examination must be considered. However, the contrast TEE is a more sensitive approach for detecting PFO than the transthoracic echocardiography. Real-time three-dimensional TEE demonstrates the dynamic morphology and en-face view of complex ASDs and hybrid defects (concomitant occurrence of a PFO with additional defects on the fossa ovalis). When there is an indication to close a complex PFO, the first choice will be ICE-guided device closure. If there is a passage of 1-20 microbubbles, the shunt is classified as small. If more than 20 microbubbles pass through the PFO, a large shunt can be diagnosed. An interatrial septal aneurysm is defined as more than 10 mm protrusion of interatrial septum toward RA.

It is important that the following factors are assessed within an echocardiographic report that evaluates the presence of a PFO:

- Size of left atrial opening
- Size of right atrial opening
- Total length of the PFO tunnel
- Presence of other defects
- Multiple openings of the PFO into the left atrium
- Atrial septum aneurysm
- Thickness of secondary septum
- Eustachian ridge/valve (or Chiari network), extent, and location.

A large PFO (≥4 mm diameter, tunnel length >14 mm), and prominent Chiari network increases the risk of cryptogenic stroke; therefore, these parameters must also be included in an echocardiography report that assesses risk stratification of patients (6).

Table 1 outlines the pros and cons of each of the diagnostic methods that can be employed to visualize the inter-atrial septum.

Table 2 provides an overview of the echocardiographic characteristics of simple and complex PFO; the latter is more prone to embolic accident and also increased ratio of device size to PFO diameter.

There are hypercoagulable states that predis-

Table1. Pros and cons of TEE and ICE.

	Requires general anesthesia	Better image resolution	Fluoroscopic time	Potential esophageal injury	Cost
TEE	YES	++	--	Yes	Low
ICE	NO	+++	Fastest method	No	High

TEE: Transesophageal echocardiography; ICE: Intracardiac echocardiography

Table 2. Echocardiographic characteristic of simple and complex PFO .

	Tunnel length	Presence of atrial septal aneurysm	Eustachian valve(measured from the border of IVC)	Thickened septum secundum>10mm	Additional multiple small defects on the fossa ovalis(hybrid)	Excessive redundant Chiari network	Excessive thickening of secondary septum
Simple PFO	<8mm	-	<10mm	-	-	-	-
complex PFO	>8mm	+	>10mm	+	+	+	+

PFO: patent foramen ovale; IVC: Inferior vena cava

pose patients to form thrombi in venous circulation. These include pregnancy and estrogen use, malignancy, surgical procedures in association with factor V Leiden (resistance to activated protein C), Antithrombin III, protein C or protein S deficiencies, antiphospholipid antibody syndrome, prothrombin mutation, and dysfibrinogenemia.

Literature review

The randomized trials that have assessed therapeutic interventions for paradoxical embolism have not produced any clear guidelines as to how best to treat this condition. Patients who have a history of ≥1 paradoxical embolism are indicated for device PFO closure. Clot removal by cardiopulmonary bypass surgery is the cornerstone of treatment; however, some studies (7,8) have reported the successful medical treatment of RA and LA clot and assessed whether the mechanical closure of PFO should be indicated. From the closure rate point of view, PFO morphology is more important than occluder size and type (8,9). Older patients are more prone to a rapid change of right heart pressure. As such, clinicians who treat members of this population must pay attention to the amount of clot burden, the co-existing hypercoagulable state, contraindications to thrombolytic drugs, and the risk of relapse. Physicians must also keep in mind the fact that if thrombi in transit are entrapped in PFO, there is a contraindication for thrombolytic therapy. One review of existing literature found that the largest thrombi in transit were 25 cm in length (10). Other reports have demonstrated that the presence of PFO is an important predictor of adverse outcome and LA dysfunction, which leads to thrombi formation in LA (10,11).

A RoPE study (Risk of Paradoxical Embolism) predicted a new ischemic cerebrovascular event in patients with PFO through the application of a risk score (13). The authors of this study illustrated that there is a higher embolic risk associated with the following features: a young patient who is a non-smoker, under 30 years old without a history of hypertension, diabetes, stroke or transient ischemic attack.

A Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) trial found that in the case of patients who have a cryptogenic (or stroke of undetermined pathogenesis) closing the PFO offers no additional benefit to alternative medical interventions (14). There is very limited data available relating to the current guidelines for secondary prevention after cryptogenic stroke. However, according to the American Heart Association guidelines, TTE (trans thoracic echocardiography) or surgical PFO closure is a Class IIa indication, the level of evidence C in patients with a prior cryptogenic stroke when the PFO appears to have high-risk features (15). A randomized trial that compared warfarin and aspirin found that there was no difference in the primary outcome that resulted from the use of these medications (16). Percutaneous closure of PFO decreases shunt severity; however, it is associated with some complications such as femoral hematoma, atrial arrhythmias, and incomplete device closure (17). Dual antiplatelet therapy with aspirin and clopidogrel is recommended for six months after device implantation.

In terms of diagnostic point, delineating right-to-left shunting through a patent foramen ovale during contrast transesophageal echocardiography is crucial. Furthermore, a review has found that the cough test is preferable to the Valsalva maneuver for ascertaining the presence of a PFO(18).

Conclusion

In conclusion, with prompt diagnosis, successful treatment of severe forms of venous thromboembolic disease with thrombi in transit complicated by paradoxical embolus can be achieved. However, according to previous reports, in-hospital mortality is as high as 44.7%. Paradoxical embolism has a higher mortality rate in patients with PTE. Increase in mortality and morbidity depends on the size of the embolus and the extent of the end-organ damage. When impending paradoxical embolism (PDE) occurs, the choice of treatment involves open-heart surgery. The therapeutic options for paradoxical embolus include thrombectomy, the use of an IVC filter, and anticoagulation.

Conflict of Interest

The authors declare no conflict of interest.

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