A review article on diagnosis and treatment of Paradoxical embolism

Abstract

One in five adults, have patent foramen ovale (PFO) and it usually cause no symptoms at all. Because of low pressure in both atria and anatomical position of the septum secundum there is no left-to-right shunting and little right to left shunting in general condition, however when the right atrial pressure rises, this slit like flap separates and allows right to the left shunting. However simultaneous occurrences of arterial emboli like as cerebrovascular accident and pulmonary embolism demonstrate the presence of paradoxical embolism through a PFO according to the Johnson criteria. (1) When a patient presents with multivascular arterial embolism, not only the contrast transthoracic echo, but also the transesophageal (TEE), real-time three-dimensional TEE and even intracardiac echocardiography (ICE) is essential to differentiate between PFO, flat atrial septal defect (ASD) and hybrid defects. There are no clear guidelines based on randomized trials for therapy of paradoxical embolism. Surgical embolectomy with exploration of the right chambers and the pulmonary arteries under full cardiopulmonary bypass is the classic treatment. Patients with a history of ≥1 paradoxical embolism may be indicated for device PFO closure.

Keywords: patent foramen ovale; Paradoxical embolism; Echocardiography
Introduction

Simultaneous occurrences of cerebrovascular accident and pulmonary embolism demonstrate the presence of paradoxical embolism according to the Johnson criteria:

((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 longstanding)) (1).

In 25–30 percent of individuals presenting with paradoxical embolism a patent foramen ovale (PFO) could be detected (2). Interatrial septum has two parts; septum primum and secundum, septum primum forms from the top of the atrium downward and septum secundum develops from the bottom of the atrium upward and to the right of the septum primum. A slit-like opening between the two parts called a PFO. Because of low pressure in both atria and anatomical position of the septum secundum there is no left-to-right shunting and little shunting in general condition, however when the right atrial pressure rises during physiologic condition like as straining, Valsalva maneuver or coughing this slit like flap separates and allows right to the left shunting. Furthermore this type of shunting may become more marked in cases where the right atrial (RA) pressure is raised due to pathology such as pulmonary embolism. There is also a “so-called” “flow phenomenon” describes a preferential blood flow from the inferior vena cava towards the atrial septum as a part of the fetal circulation.

There are some case reports of coexistence of paradoxical emboli with pulmonary, (PE) systemic embolism and deep vein thrombosis (DVT) especially in patients with “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 had a PFO (5), which is the most common cardiac defect in association with paradoxical embolism.
When a patient presents with multivascular arterial embolism, not only the transthoracic echo (TTE), but also the transesophageal (TEE) and even intracardiac echocardiography (ICE) is essential to differentiate between PFO, flat atrial septal defect (ASD) and hybrid defects. TTE cannot differentiate between PFO and ASD, and not suitable for guiding device closure of PFO, however with contrast echo (agitated saline injection) during Valsalva maneuver at the time of contrast injection a right to left shunt could be diagnosed. When contrast bubbles appeared in the right atrium, the patient was asked to quickly stop straining. If bubble passed 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 considered, however contrast TEE is more sensitive approach for detection of PFO. Real-time three-dimensional TEE demonstrate 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 passage of 1-20 microbubbles shunt classified as small and if more than 20 microbubble pass through the PFO a large shunt could be diagnosed. Interatrial septal aneurysm is defined as more than 10 mm protrusion of interatrial septum toward RA.

In an echocardiographic report for the presence of a PFO this check list must be mentioned.

- 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 increase the risk of cryptogenic stroke, therefore, these parameters must be included in echocardiography report for risk stratification of patients (6).

Table 1 outlines the pros and cons of each diagnostic method for visualization of inter-atrial septum.

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

**Table 1.** pros and cons of TEE and ICE

<table>
<thead>
<tr>
<th></th>
<th>Requires general anesthesia</th>
<th>Better image resolution</th>
<th>Fluoroscopic time</th>
<th>Potential esophageal injury</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEE</td>
<td>YES</td>
<td>++</td>
<td>--</td>
<td>yes</td>
<td>low</td>
</tr>
<tr>
<td>ICE</td>
<td>NO</td>
<td>+++</td>
<td>Fastest method</td>
<td>no</td>
<td>high</td>
</tr>
</tbody>
</table>

TEE: transesophageal echocardiography; ICE: intracardiac echocardiography

**Table 2.** Echocardiographic characteristic of simple and complex PFO

<table>
<thead>
<tr>
<th>Tissue bridge length</th>
<th>Presence of atrial septal aneurysm</th>
<th>Eustachian valve(measured from the border of IVC)</th>
<th>Thickened septum secundum&gt;10 mm</th>
<th>Additional multiple small defects on the fossa ovalis(hybrid)</th>
<th>Excessive redundant Chiari network</th>
<th>Excessive thickening of secondary septum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple PFO</td>
<td>&lt;8mm</td>
<td>&lt;10mm</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Complex PFO</td>
<td>&gt;8mm</td>
<td>&gt;10mm</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

PFO: patent foramen ovale; IVC: Inferior vena cava

There are hypercoagulable states which predispose patients to form thrombi in venous circulation such as 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**

There are no clear guidelines based on randomized trials for therapy of paradoxical embolism. Patients with a history of ≥1 paradoxical embolism are indicated for device PFO closure. Clot removal by cardiopulmonary bypass surgery is the cornerstone of treatment however there are reports (7, 8) of successful medical treatment of RA and LA clot and whether 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 rapid change of right heart pressure, and in this special population clinicians who care about patients must pay attention to the amount of clot burden, and co-existing hypercoagulable state, contraindications to thrombolytic drugs, and the risk of relapse. It must also keep in mind that if thrombi in transit are entrapped in PFO, there is contraindication for thrombolytic therapy. In a review of literature the largest thrombi in transit was 25 cm in length.

There are some reports demonstrate that presence of PFO is an important predictor of adverse outcome and LA dysfunction which leads to thrombi formation in LA (10, 11).

There is a RoPE study (Risk of Paradoxical Embolism) which could predict a new ischemic cerebrovascular event in patients with PFO by a risk score (13). Authors of this study illustrate that there is higher embolic risk associated with these features: a young patient who is non smoker, under 30 years old without history of hypertension, diabetes, stroke or transient ischemic attack.

RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial showed in patients with a cryptogenic
(or stroke of undetermined pathogenesis) stroke, there is no benefit of closure of a PFO in comparison with medical therapy (14). There is very limited data according to current guidelines for secondary prevention after cryptogenic stroke. However according to American Heart Association guidelines Percutaneous or surgical PFO closure is a class IIa indication, level of evidence C in patients with a prior cryptogenic stroke when the PFO appears to have high-risk features (15). In a randomized trial which compared warfarin against aspirin there was no difference in the primary outcome (16). Percutaneous closure of PFO decrease shunt severity but it is associated with some complications like as femoral hematoma and atrial arrhythmias and incomplete device closure (17). Dual antiplatelet therapy with aspirin and clopidogrel is recommended for 6 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 and there is a review which showed that cough test is preferred over Valsalva maneuver to demonstrate the presence of a PFO (18).

**Conclusion**

In conclusion, with prompt diagnosis, successful treatment of severe form of venous thromboembolic disease with thrombi in transit complicated by paradoxical embolus could be achieved; However according to previous reports in-hospital mortality is as high as 44.7% (17,18). Paradoxical embolism has higher mortality in patients with PTE. Increase in mortality and morbidity depends on the size of the embolus and end-organ damage (19,20). 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.
References


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