Paradoxical Emboli: the Relationship between Patent Foramen Ovale, Deep Vein Thrombosis and Ischaemic Stroke

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Introduction

Paradoxical emboli (PDE) were first described by Conheim in 1877 and defined as the passage of venous thrombotic material through a right-to-left intracardiac shunt into the arterial circulation. Until 1930, PDE was a postmortem diagnosis made by visualising a venous thrombus lodged through an intracardiac defect. Current techniques of contrast angiography and echocardiography have improved the diagnosis of intracardiac defects enabling the diagnosis of PDE to be made during life. Several investigators have recently recognised a subset of patients who suffer a non-haemorrhagic stroke with no identifiable risk factors. In this population PDE have been implicated as the cause of stroke. However, unless a thrombus is visualised within an intracardiac defect, the diagnosis is only presumptive. In 1972, Meister et al. proposed the following clinical criteria for the diagnosis of PDE: (1) an arterial embolism, (2) the presence of venous thrombosis, (3) the presence of an intracardiac defect, and (4) a transient reversal of the intracardiac shunt. The true incidence of PDE remains undefined. However, according to the available data, deep venous thrombosis (DVT) is responsible for more than 200 000 hospital admissions in the U.S.A. every year. The incidence of patent foramen ovale (PFO) in the general population being 20–35%, 70 000 patients are theoretically at risk for a PDE every year.

Incidence and Prevalence

The true incidence of PDE is difficult to establish. The diagnosis is usually made in young patients with no identifiable embolic source and who meet the four criteria proposed by Meister. Contrast echocardiography is now an efficient and non-invasive modality for the study of intracardiac defects. In 1988, two studies conducted by Webster et al. and Lechat et al. reviewed the prevalence of PFO in young patients with no identifiable risk factors who suffered a cerebrovascular accident. Lechat showed that PFOs were present in 40% of young patients with strokes and no risk factors, in 21% of patients with strokes and no risk factor, and in 10% of the control group (no strokes). Similarly, Webster et al. demonstrated the presence of PFOs and right-to-left shunting during a Valsalva manoeuvre in 50% of patients less than 40 years old who had suffered a non-haemorrhagic stroke compared to 15% in the control group. The mere presence of a PFO and an intermittent right-to-left shunt cannot establish the diagnosis of PDE. However, these studies have stimulated great interest in the evaluation of the patient who suffers a cryptogenic embolic event. Thompson and Evans, in a large necropsy study involving more than 1000 cadavers, demonstrated that 6% had a pencil patent PFO and 21% had a probe patent PFO. Analysis of the data provided by the Michael Reese stroke registry showed that 36% of patients presenting with infarction secondary to a cerebral embolism had no identifiable source of embolisation. Knowing the incidence of PFO in
the general population, we can infer that 12% of ischaemic strokes may be potentially a result of a PDE. In addition, Stollberger et al. have demonstrated that the incidence of DVT in a population with PFO and stroke is 57%. As a result, up to 7% of patients less than 50 years old who suffer an embolic stroke meet Meister’s criteria for PDE.

Clinical presentation and pathophysiology

The sources of paradoxical venous thromboemboli include the inferior vena cava, its tributaries, and the right heart chambers. Interestingly, some reports have documented cases of paradoxical amniotic fluid emboli, air emboli, and fat emboli. As mentioned previously, Stollberger showed that 57% of patients with suspected PDE and no other source of embolisation had a DVT diagnosed by venography. Approximately half of these patients had only calf vein thrombosis and 86% had no clinical evidence of DVT. In contrast, Ranoux et al. in a review of 32 patients with known PFO and ischaemic stroke, found the incidence of DVT to be extremely low and concluded that PDE was not the mechanism of stroke in patients with PFO. However, in their study, only 13 of 32 patients underwent venography, as patients with risk factors for strokes were excluded. In addition to the fact that up to 30% of patients with PDE had no evidence of venous thrombosis on venography, DVT appears to be frequently unrecognised in this patient population.

The presence of an intracardiac defect with a right-to-left shunt is a prerequisite for the diagnosis of PDE. Pulmonary emboli (PE), leading to an acute elevation of the right heart pressure, has classically been considered a precondition for PDE. However, similar haemodynamic conditions can be observed in patients with chronic obstructive pulmonary disease and pulmonary hypertension leading to a chronic right-to-left shunt. Furthermore, acute right-to-left shunting has been demonstrated by contrast echocardiography during systole or during a Valsalva manoeuvre.

In Loscalzo’s review, 60% of patients with PDE suffered a PE documented by high probability radionuclide scan or a positive pulmonary angiogram. PDEs have lodged in all segments of the arterial tree. The cerebral circulation is the most commonly involved site (37–50% of the reported cases). Other involved sites include visceral (6–9%), coronary (7–9%), upper extremity (25%), and lower extremity arteries (30%). Multiple sites are involved in up to 32% of the patients.

Diagnostic strategies

The diagnosis of PDE is usually based on established criteria and the failure to identify an arterial or cardiac embolic source. Arteriography remains the best tool to identify the presence of a proximal arterial lesion. Transoesophageal echocardiography (TEE) is the most sensitive non-invasive test for the detection of atrial septal defects which are commonly missed by trans-thoracic echocardiography. A contrast TEE cannot only determine the size of a PFO, but also quantify the degree of shunting. The term contrast echocardiography refers to the reflective property of micro-cavitation bubbles produced by mixing a saline solution with air. Commonly, at least four injections in the peripheral venous system are made during quiet breathing and after a Valsalva manoeuvre. When a PFO or an other atrial septal defect is present, the microbubbles can be visualised in the right atrium and in the left atrium or ventricle 2 to 3 cardiac cycles later. Another adjunct to contrast TEE is the cough test proposed by Stoddard et al. This test, consisting of 5 rapid succession coughs after the appearance of the microbubbles in the right atrium, was found to be significantly superior to quiet breathing or the Valsalva manoeuvre. Teague et al. have proposed the use of transcranial Doppler ultrasound to detect interatrial shunting. This technique has the advantage of detecting interatrial shunting and target organ involvement in patients suspected to have paradoxical cerebral embolisation.

Following exclusion of an arterial or cardiac source of embolisation, an effort should be made to establish the presence of a venous thrombosis. Ultrasonography is now the modality of choice for the evaluation of the deep venous system with an accuracy greater than 95% for proximal DVTs. Its major limitation remains in the diagnosis of calf vein thrombosis. Tibial vein thrombosis has been shown to be associated with PE detected by radionuclide scans in 20–30% of asymptomatic patients. These PEs would normally remain asymptomatic, as they undergo spontaneous lysis in the pulmonary circulation. However, in the patient with a PFO, embolisation of calf vein thrombus may be a disastrous event; therefore, contrast venography is still recommended to establish the diagnosis of DVT in patients suspected to have a PDE.

Treatment options

The management of PDE remains varied in the literature and no single algorithm has been established.
for this complex entity. Classically, anticoagulation and some form of caval interruption has been recommended. Full-dose anticoagulation with heparin continues to be the most commonly used therapy for the treatment of DVT and haemodynamically stable PE. However, it has been shown that patients with PE treated with heparin alone have a 9% incidence of recurrent embolisation into the pulmonary vasculature. The true incidence of recurrent embolisation may actually be higher as the occurrence of asymptomatic events would be difficult to estimate. In Stollberger's study five patients with PFO and DVT treated with heparin alone experienced a stroke and one developed a brachial artery embolism. Katz et al., in a large review, noted a PDE recurrence rate of 30% in patients treated with various forms of caval interruption and heparinisation. This high recurrence rate may be attributed to the inability of caval filters to prevent the passage of emboli less than 3 mm in size. We recently published our current approach to PDE in the peripheral arterial system, excluding the cerebral circulation, associated with PE. Briefly, we recommend, for the patient with a non-threatened limb, the placement of a caval filter followed by intra- pulmonary thrombolysis with or without intra-arterial lytic therapy. The benefit of this approach is the rapid resolution of the right-to-left shunt, reducing the risk of preventing further PDE. In patients with threatened limbs, the best option remains surgical embolectomy followed by caval filter placement and anticoagulation. We still recommend surgical or endovascular PFO closure for the long-term prevention of PDE. Patients presenting with PDE to the cerebral circulation are difficult to manage, as the use of thrombolytic therapy in these cases remains experimental with inconclusive results. We continue to recommend anticoagulation therapy with caval filter placement for this group of patients followed by endovascular or surgical closure of the septal defect.

Conclusion

The current data suggest that PDE may be responsible for a significant number of ischaemic events in younger patients who present with strokes and PE. Contrast echocardiography, a simple non-invasive tool, has improved our ability to diagnose PFO and lay the ground for a more aggressive approach to the diagnosis of PDE. Closure of the PFO is the most effective approach, as heparin therapy and caval interruption have failed to eliminate the risk of recurrence. DVT prophylaxis remains our best weapon to prevent PDE.

References

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