Acute Pulmonary Embolism and Paradoxical Embolism in Patients with Patent Foramen Ovale: To Close or Not to Close… That is the Question!

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Abstract

Nowadays, the treatment of patent foramen ovale (PFO) after acute pulmonary embolism (PE) remains matter of speculation. Absence of both randomized trials and recommendations in current international guidelines complicate the decisions making in such patients. In the present manuscript we discuss about the reasons for which PFO should be closed after acute PE.

Keywords: Patent Foramen Ovale; Pulmonary Embolism; Endovascular treatment

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Introduction

Several studies have already proposed and analysed the role of patent foramen ovale (PFO) in different clinical settings; cryptogenic stroke, peripheral and coronary paradoxical embolism, migraine with aura, and others. However, the PFO closure in pulmonary embolism (PE) patients remains one of the most intriguing for different reasons. Firstly, current international guidelines on acute PE no takes into account neither PFO or others atrial septum defects. Secondly, previous data were obtained from studies based on different PE classifications, as the Miller's index, which is not currently used in the medical practice. Obviously, also the absence of any studies and/or trial on the role of PFO closure in PE patients contributes to this uncertainty. Because PFO is often asymptomatic, PE patients could receive the diagnosis during the management of the acute event [1]. In this manuscript, we review the reasons for which PFO should be closed after PE also presented a clinical case.

Evidence from the literature

As well known, stroke and PE are currently the second and third leading causes of cardiovascular mortality in western countries. For these reasons, it is quite intuitive that the presence of PFO in PE patients could be a serious problem both in the short- and long-term periods. If PE appears concomitantly with PFO, the abrupt elevation of pulmonary artery pressure (PAP) and also the increase in pulmonary vascular resistance can promote an inverse shunting across the PFO [2], resulting in an increased risk of systemic paradoxical embolization (PDE) [3]. Indeed, in this respect, Thomas et al. observed that PDE complicate PE in 67% of cases [4]. In PE patients, PFO are generally detected with transthoracic echocardiography (TTE) [5]. However, the clinical suspicion could arise also from the patient's medical history. Further investigation in PE patients should be performed in the presence of previous suggestive signs and/or symptoms, as migraine, migraine-like symptoms, previous stroke or transient ischemic event of undefined etiology and previous systemic

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embolism of undefined origin [6]. Because PFO could be often asymptomatic a depth TTE evaluation is recommended in case of inconclusive results at TTE. Moreover, the use of trans-esophageal echocardiography (TEE) has been shown to be more sensitive improving the PFO diagnostic accuracy. Nowadays, a simple venous contrast study, called "bubble test", which is based on the injection of a shaken saline solutions into a peripheral vein, have demonstrated a higher sensitivity and specificity versus the traditional Doppler techniques in detecting PFO. Transcranial Doppler with bubble test is considered the most sensitive non-invasive diagnostic tool for PFO detection and quantitative assessment.

Previous studies, which analysed the relationship between PFO and PE, assessed that echocardiographic PFO detection signifies a higher risk of death and/or thromboembolic complications [6]. In particular, patients with a PFO greater than 4mm have 10-fold risks of death and 5-fold risks of systemic embolism compared to patients without PFO [7]. A recent study, which considered PE patients classified as intermediate-risk, revealed a PFO prevalence of 17.7 % [8]. On the contrary, a lower percentage have been found from Clergeau et al. in PE patients classified as low-risk PE [9]. Nowadays, despite seems that the prevalence of PFO increases with the severity of PE, due to the absence of definitive results, the real prevalence of PFO among the different PE risk groups remains matter of speculation.

PE implies an imbalance between the ventilation/perfusion ratio of the lungs. In particular, hypoxaemia in PE is due to the increased V/Q mismatch which is not associates with increased shunt. Generally, patients with hypoxaemia are not refractory to oxygen administration, apart in case of high risk (or massive) PE, which is associated with a severe ventilation/perfusion mismatch. In the other cases, a refractory hypoxaemia could contribute to raise the suspicion of the presence of alternative or complementary causes as PFO.

The latest European Society of Cardiology (ESC) guidelines on acute PE marginally takes into account the presence of PFO in PE patients. Indeed, it is only recommended to consider the presence of PFO when thrombolytic treatment must be performed. More in general, current international guidelines and consensus paper on PE reveal a lack of recommendation about the clinical and/or interventional management of PFO in PE patients. On the contrary, an interesting recommendation comes from Doyen at al. which suggested that PFO screening should be integrated into the decision algorithm for thrombolysis in PE patients [8]. However, the main question remains: "Should these patients be treated only with medical therapy after the acute event?" Is percutaneous PFO closure recommended? Answers are actually controversial. In the real world, although the majority of patients after acute PE are treated with oral anticoagulation, only few patients underwent to PFO closure. Why? Probably because most physician believed that the oral anticoagulation could be enough as secondary stroke prevention in these patients, despite some of those already presented single or multiple previous ischemic events at the time of PFO diagnosis. As general rule, before clinicians decide if PFO closure it is necessary to consider the risk-to-benefit ratio. A recent review of non-randomized trials suggested that the rate of recurrence of stroke was lower with PFO closure compared to medical treatment [10]. For this purpose, PFO percutaneous catheter closure can be proposed in patients with recurrent stroke therapy to avoid future PDE.

The magnitude of the problem posed by PDE in patients with PE and PFO, coupled with the continued uncertainty regarding the optimal approach to secondary prevention underscores the critical need for a general consensus on the best treatment.

Role of hypercoagulable state:

A hypercoagulable state has been described both in patients with previous CS stroke and/or PE. About thirty-one percent of patients with CS have a hypercoagulable state; on the contrary, the real prevalence of thrombophilic mutations in PE has not been defined, because thrombophilic screening is actually not recommended as a part of the work-up in all patients with PE. The thrombophilic assessment could be another useful parameter to evaluate whether to close or not to close PFO and/or to start anti-thrombotic regimen. In clinical practice, the presence of known hypercoagulable states with recognised increased risks of thrombosis/embolism despite recommended warfarin treatment (lupus anticoagulant/antiphospholipid antibody syndrome) is an indication for primary PFO closure. In patients with PFO, thrombophilic states may increase the occurrence of venous clots that can paradoxically embolize to the systemic circulation.

Suggested Recommendations:

We believe that the choice to close the PFO should be recommended and also individualized at the same time. Obviously, the potential benefits of endovascular treatment should be weighed against the procedure risks and patient's comorbidities. Generally, patients with cryptogenic cerebral ischemic events are at higher risk of silent PE [11]. Moreover, PE, especially if temporally correlated with an ischemic event, could influence the patient treatment (anticoagulation ± closing PFO). Based on these observations, we would recommend that patients with PFO and thrombophilia be strongly considered for Transcatheter PFO closure and then for chronic oral anticoagulation.

Declarations of Interest:

The authors declare no conflicts of interest.

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The authors state that they abide by the "Requirements for Ethical Publishing in Biomedical Journals" [12]

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