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Review

Percutaneous patent foramen ovale occlusion: Current evidence and evolving clinical practice

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ABSTRACT

Patent foramen ovale (PFO) has long been implicated with cryptogenic stroke, migraine and decompression illness. PFO is common and its implicated pathologies cause devastating neurological sequelae; and hence have drawn the attention of medical practitioners across disciplines. The pathogenesis is hypothesized to be caused by micro-emboli or neuro-hormones which would otherwise being filtered by the lungs, astraying into the systemic circulation via the atrial communication especially during Valsalva maneuver. Treatment options have been proposed; among others are medical therapy, PFO closure or both. While medical therapy as secondary prevention is being adopted by most centers in the world, PFO closure is performed in selected patients only. The reason being is that most studies linking PFO to these pathologies are observational in nature. And these associations do not equate to a firm cause and effect relationship. For causal relationship to be established, good quality prospective data is required. Recently, there has been emergence of new prospective trials which improve the understanding of PFO closure in these pathologies. This article reviews the associations between PFO and the three main implicated pathologies as well as the evidence for PFO closure in the current era.

1. Introduction

Foramen ovale typically closes spontaneously as the left atrial pressure increases with simultaneous drop in the right atrial pressure, opposing each side of the interatrial septal flap in the process during postnatal circulatory adaptation. Nonetheless, total closure does not occur in everyone (Fig. 1).

The incidence of patent foramen ovale (PFO) has been studied both in vitro and in vivo. In an autopsy audit on 965 specimens, the overall incidence of PFO was noted to be 27% [1]. The incidence drops from 33% in those <30 years old to 20% in adults >80 years old. Meanwhile, one may argue that having a PFO in the postmortem does not equate to it being patent in vivo as the PFO may be prod open in pathological specimen yielding a higher prevalence. In 1999, Meissner et al in her study of 585 randomly selected patients 45 years and above using transesophageal echocardiography (TEE) without contrast showed a prevalence of 26% of PFO in the population [2], which concurs with the findings of the in-vitro study. In a similar study looking at 1100 multi-ethnic population of northern Manhattan, the incidence PFO of non-stroke subjects above 35 years old using transthoracic echocardiography with contrast was lower at 14.9% [3]. The prevalence has no preponderance to either gender [4].

PFO has been implicated for causing cryptogenic stroke, migraine and decompression sickness. Primary surgical closure of PFO is almost never performed in the current era. It has been substituted by percutaneous approach which is easy to perform and has low complication rates [5,6]. Rashkind first mooted the idea of patent foramen ovale occlusion after the success of transcatheter atrial septal defect closure [7]. Two decades later, transcatheter PFO closure has become one of the commonly performed procedures in the adult congenital heart population in the United Kingdom [8]. This article aims to review and summarize the available data on the three main indications for transcatheter PFO closure in the current era, namely cryptogenic stroke, migraine and decompression illness.

1.1. Cryptogenic stroke

Cryptogenic stroke is a stroke with no apparent cause and accounts for 15%–40% of total ischemic stroke [9–11]. Studies have shown a higher prevalence of PFO, especially those with atrial septal aneurysm (ASA) in patients with cryptogenic stroke. [Figs. 2–3] ASA describes hypermobility of redundant primum septum tissue. In a stricter sense, ASA is termed when there is excursion of the redundant septal tissue to either side of the atria from the septal plane for more than 10 mm

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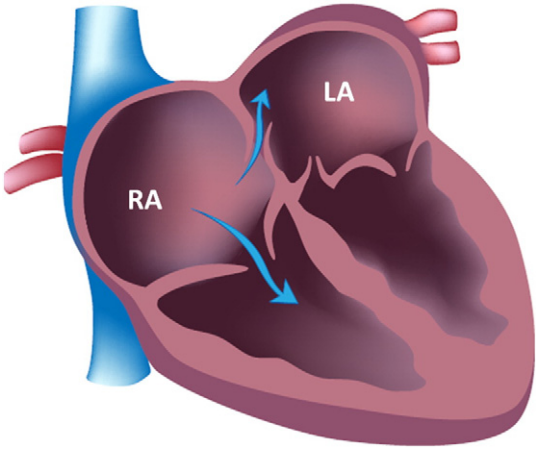

Fig. 1. PFO allows right to left shunting during transient rise of right atrial pressure during release of Valsalva maneuver, a frequent daily maneuver performed during sneezing, coughing and straining. The resultant right to left shunting allows transgression of microemboli and neuro-hormones, responsible for cryptogenic stroke, migraine and decompression sickness, which would otherwise be filtered by the lungs to reach the systemic circulation.

[12]. It is unsure as why cryptogenic stroke is associated with ASA although various speculations have been made.

1.2. Association between PFO and cryptogenic stroke

The association between PFO and cryptogenic stroke began with observational studies which showed higher incidence of PFO in patients with cryptogenic strokes [13–15]. However, these observational studies have small sample size with the largest having 65 patients, and hence were not powered to draw any concrete conclusion.

Meta-analysis of case control studies by the Glasgow group reported odds ratios of cryptogenic stroke for all ages were 1.83 (95% CI, 1.25–2.66) in the presence of PFO, 2.35 (95% CI, 1.46–3.77) for ASA, and 4.96 (95% CI, 2.37–10.39) for PFO plus ASA [16]. The odd of PFO being associated with cryptogenic stroke is even higher if the patient is less than 55 years old and has both PFO and ASA. More recently, Davies et al performed another meta-analysis looking at PFO and its association with migraine and cryptogenic stroke and found similar weak association between PFO and cryptogenic stroke (hazard ratio: 1.6; 95% CI 1.0–2.5; odds ratio: 1.3; 95% CI 0.9–1.9) [17]. Bearing in mind that these studies are meta-analysis in nature, they do not correct for confounding bias between studies and hence more prospective studies were conducted.

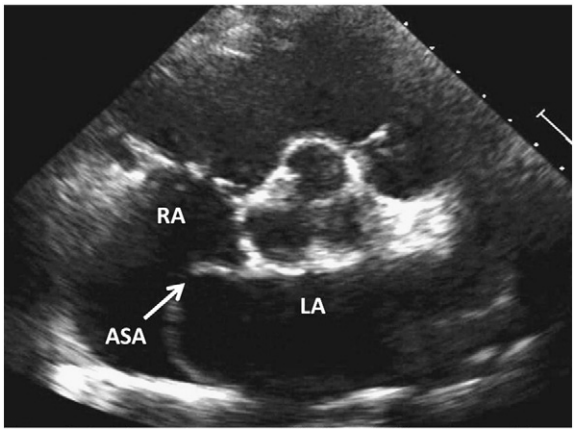

Fig. 2. Atrial septal aneurysm (ASA) — thin, flimsy interatrial septum which is aneurysmal, swinging between both atria throughout the cardiac cycle. RA: right atrium; LA: left atrium.

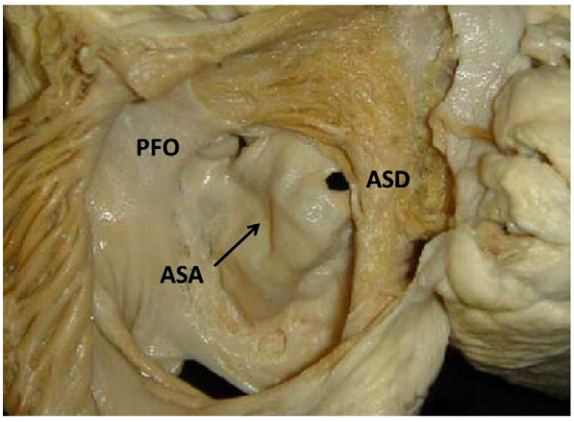

Fig. 3. ASA viewed from the right atrium. It forms redundant aneurysmal septum between the atria. This septum is fenestrated by an atrial septal defect (ASD) and a patent foramen ovale (PFO).

1.3. Prospective study linking PFO and first cryptogenic stroke

The Stroke Prevention: Assessment of Risk in a Community (SPARC) and the Northern Manhattan Study (NOMAS) are the two major studies that prospectively examine the association between PFO and cryptogenic stroke. In the SPARC study, 585 randomly sampled subjects above 45 years old were followed up for a median duration of 5.1 years [18]. PFO was found not to be an independent predictor of stroke. However, the risk of a cerebrovascular event among subjects with ASA was apparently, nearly four times higher than that in those without ASA (hazard ratio 3.72, 95% confidence interval 0.88 to 15.71, $p = 0.074$). Meanwhile, in the NOMAS, where 1100 non-stroke subjects older than 39 years old were followed up prospectively for a mean duration of 6.7 years, hazard ratio of cryptogenic stroke with PFO was 1.64 (95% CI, 0.87–3.09) and with ASA was 3.66 (95% CI, 0.88–15.30) [19]. The coexistence of PFO and ASA, in this study did not increase the stroke risk (adjusted hazard ratio 1.25, 95% CI 0.17 to 9.24). Both these trials have failed to achieve statistical significance and being prospective in nature, the actual patients with PFO and ASA in these 2 studies were small. There were 127 and 11 in SPARC and 164 and 27 in NOMAS of patients with PFO and ASA, respectively. The small number of patients with ASA undoubtedly cast shadow over the strength of analyses in these studies which may partly explains the difference in the conclusion. Moreover, the mean age of the subjects in both studies is above sixties, in who may have confounding factors such as hypertension and intermittent transient arrhythmias which by themselves, are risk factors for ischemic stroke. These prospective studies were considered flawed and under-powered, hence definite association of PFO to cryptogenic stroke still eludes us.

1.4. PFO and recurrent stroke

In terms of its risk for recurrent stroke, a study across 30 centers across Europe, investigating the 581 patients with cryptogenic stroke prospectively found no significant risk in recurrent stroke patients with either PFO or ASA [20]. However, if both PFO and ASA are present, the risk is 15.2% (95% CI, 1.8–28.6). More recently, Kitsios and Serena et al studied the effect of PFO in causing recurrent stroke separately by investigating the importance of right to left shunting, the hypothesized culprit behind the role of PFO in causing stroke. Kitsios et al looked into MRI evidence of silent stroke and stroke of different radiological age and their relationship with clinical indicators of paradoxical embolism in a prospectively collected Tuft Stroke Registry [21]. No association between the two found. Serena and co-workers identified 200 patients with massive right to left shunting in 486 patients with history of cryptogenic stroke and found no association between PFO with massive right to left shunting and PFO [22]. All patients were being treated with Aspirin throughout the study period. In a