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Patent foramen ovale and cryptogenic stroke

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ABSTRACT

The presence of a patent foramen ovale (PFO) has been found to be associated with an increased risk of cryptogenic stroke in many case–control studies. This paper reviews the current understanding of the pathophysiology and diagnosis of PFO, and therapeutic options of patients with PFO and cryptogenic stroke.

Key words: Antithrombotic treatment, Cryptogenic stroke, Echocardiography, Patent foramen ovale.

Introduction

The foramen ovale is a remnant of the fetal circulation that remains open as a patent foramen ovale (PFO) in approximately 25% of the general adult population [1,2]. Although the risk of ischemic stroke related to the presence of PFO has been established by many case–control studies [3–6], such risk appears low in the general population. Lack of demonstration of stroke risk from the presence of PFO in general population points to an extremely small chance of stroke from the presence of PFO. Paradoxical embolization of venous thrombi through a PFO is hypothesized to explain the association between PFO and stroke. Therapeutic strategies have been developed to prevent the recurrent thromboembolic events in patients with PFO. Based on the results of three large published randomized trials and meta-analyses of these three trials, current guidelines do not yet recommend percutaneous PFO closure [7,8]. Even after the approval of an occlusion device for stroke prevention by FDA [9], considerable controversy remains. In this review, we will describe the prevalence, diagnosis, and clinical associations of PFO, as well as the preventive strategies to decrease the risk of recurrent stroke in cryptogenic stroke patients with PFO.

Prevalence

The foramen ovale is a normal component of the fetal circulation that usually closes after birth by the fusion of the two embryologic components of the atrial septum: the septum primum and septum secundum. In many subjects, a small communication persists into adult life, and is referred to as a PFO. The prevalence of a PFO in the healthy adult population ranges from 15% to 35% on autopsy studies and 15% to 25% on echocardiographic studies [1,2]. One study of 965 autopsy cases documented an increasing size and decreasing prevalence of PFO with age (34.3% up to 30 years, 25.4% in the fourth to eighth decade and 20.2% in the ninth and tenth decades) [1]. Gender [1,2] and race-ethnic [10] differences are not apparent in the prevalence of PFO, although large PFO is more frequently observed in Whites and Hispanics compared with Blacks [10].

Diagnosis

The diagnostic imaging techniques most commonly used for PFO detection are transthoracic echocardiography (TTE) and

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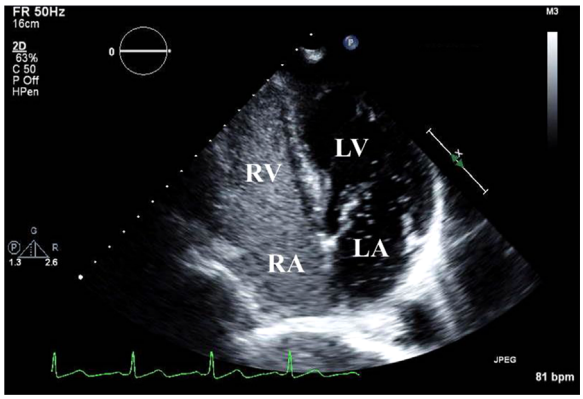

Fig. 1 – Example of positive contrast study by TTE in a patent with PFO. Microbubbles are visualized filling the right-sided chambers and into the LA and LV. LA, left atrium; LV, left ventricle; PFO, patent foramen ovale; RA, right atrium; RV, right ventricle; TTE, transthoracic echocardiography.

transesophageal echocardiography (TEE), both of which can be carried out with the use of intravenous contrast agent injection to diagnose right-to-left shunting. It is recommended that the saline contrast be composed of 9 mL of normal saline agitated with 1 mL of room air, agitated back and forth between two sterile syringes just before intravenous bolus injection through a forearm vein [11]. The injections should be performed at rest and with provocative maneuver to increase the right atrial (RA) pressure, such as cough and Valsalva maneuver. It is important to identify deviation of the interatrial septum to the left atrial (LA) side, confirming elevation of RA pressure. The presence of PFO is presumed when agitated saline contrast is noted in the LA within three cardiac cycles after complete opacification of the RA (Fig. 1). If late appearance of microbubbles is noted, it is presumed to occur as a result of intrapulmonary shunt. In addition to agitated saline contrast, several solutions are also useful for the detection of right-to-left shunt in subjects with suspected PFO [12,13].

TEE is considered the gold standard for the diagnosis of PFO because of its higher diagnostic accuracy, but, due to its semi-invasive nature, it is usually reserved to cases in which a better anatomic definition of atrial septum is needed. TEE allows for direct visualization of PFO opening and separation between the septum primum and secundum (Fig. 2A). The shunting of blood across the PFO can often be visualized by color flow Doppler (Fig. 2B). Fig. 2C shows right-to-left shunt through the PFO with the administration of intravenous contrast agents.

Contrast transcranial Doppler (TCD) is also used to detect a PFO. This technique is usually carried out at the neurologist's office in patients with an unexplained cerebrovascular event. The sensitivity of contrast TCD has been shown to be close to that of TEE [14]. Though rarely used, ear oximetry with Valsalva maneuver may be useful as a screening method for PFO detection [15].

PFO and risk of ischemic stroke

Among ischemic strokes, approximately 30–40% are cryptogenic. The relationship between PFO and cryptogenic stroke was initially described in younger patients [3,4]. The association between PFO and cryptogenic stroke in older patients has previously been described [5] and a large TEE study has more recently confirmed this association [6]. In this TEE study, PFO was significantly more frequent in patients with cryptogenic stroke than in those with stroke of determined cause in both the younger subgroup (43.9% vs. 14.3%) and the older subgroup (28.3% vs. 11.9%). After adjustment for other stroke risk factors, PFO remained strongly associated with cryptogenic stroke in the older group [odds ratio (OR) = 3.00; 95% confidence interval (CI): 1.73–5.23; $p < 0.001$] [6].

Although the risk of ischemic stroke related to the presence of PFO has been established by many case–control studies, such risk appears very low in the general population. In the Stroke Prevention: Assessment of Risk in a Community (SPARC) study, the stroke risk from cardiac embolic sources was investigated by TEE [16]. The prevalence of PFO was 24% and over a median follow-up of 5 years, PFO was not associated with increased risk of cerebrovascular events [hazard ratio (HR) = 1.46; 95% CI: 0.74–2.88]. In the population-based Northern Manhattan Study (NOMAS), the presence of a PFO was evaluated by contrast TTE in 1100 stroke-free subjects [17]. The prevalence of PFO was lower (15%) compared to previous study, reflecting the lower sensitivity of TTE. Over a mean follow-up of 11 years, PFO was not independently associated with ischemic stroke (HR = 1.10; 95% CI: 0.64–1.91). These two studies demonstrate a low risk of initial stroke from the presence of PFO in general population although SPARC study has relatively short follow-up

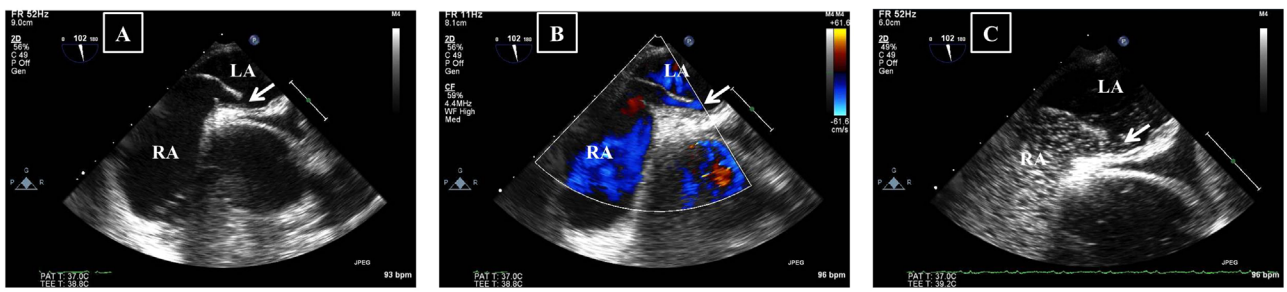

Fig. 2 – Diagnosis of a PFO by TEE. (A) Direct visualization of PFO by TEE. The septal separation is visible (arrow). (B) TEE visualization of shunt through the PFO (arrow) by color Doppler. (C) Agitated saline contrast study of TEE. Microbubbles are seen entering the LA through the PFO (arrow). LA, left atrium; PFO, patent foramen ovale; RA, right atrium; TEE, transesophageal echocardiography.