

Treatment of Foramen ovale with Stroke Patients: A Review

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1. Abstract

Foramen ovale is a physiological channel during the embryonic period of the atrial septum of the heart, which allows umbilical vein blood to flow from the right atrium into the left atrium to maintain fetal blood circulation. If the foramen ovale is still not closed at the age of more than 3 months, or if there is a shunt at the atrial level, it is called Patent Foramen Ovale (PFO). The unclosed foramen ovale is composed of primary septum and secondary septum, with long primary septum and short secondary septum, forming a piece of valve. when the valve is open, it can pass through the blood flow and can be diverted in both directions under the action of pressure. Many studies have shown that the existence of PFO shunt is closely related to cryptogenic stroke, so the choice of upper foramen ovale closure or drugs has been concerned. This article reviews the treatment of patent foramen ovale.

2. Anatomical and Circulatory Effects

The oval fossa is located in the middle and lower part of the atrial septum. In the period of embryonic development, the atrial septum occurs successively as primary septum and secondary septum, the secondary septum is located in the right atrial surface of the oval fossa, and the remaining primary septum is located in the left atrial surface of the oval fossa, which acts as a membranous valve, also known as the foramen ovale valve. The primary septum is thin, and the free semilunar margin forms an oval pore on the second septum, which is an oval pore. During the embryonic period, the pressure of the right atrium was higher than that of the left atrium, and the oxygenated blood of the right atrium entered the left atrium from the foramen ovale oblique upward through the second atrial foramen of the primary septum. The pulmonary circulation

begins to work after birth, and the pressure of the left atrium is higher than that of the right atrium, resulting in the functional closure of the foramen oval. With the increase of age, the valvular adhesion of foramen ovale was stiff, the activity was weakened, and the fibrous tissue proliferated, so that the pore was completely plugged. In most people, about 3 months after birth, the secondary septum and foramen ovale flap fuse together to form a permanent atrial septum, and some people leave permanent defects and form PFO. PFO is one of the most common congenital heart diseases in adults, and about 25% of normal people have PFO [1].

In 1877, the German pathologist Cohnheim found the death related to PFO [2], and Zahn formally put forward the concept of abnormal embolism in 1885, PFO began to attract the attention of experts and scholars. After more than 100 years of changes, with the development of ultrasound imaging, not only thrombus at PFO was found at autopsy, but also there were reports of riding across the thrombus in vivo. In 1985, Nellessen et al. [3] confirmed the straddle thrombus at PFO for the first time, and in 1994, Brogno et al. [4] found straddle thrombus at PFO and blood clots were detected in the left and right atrium, which provided direct evidence for abnormal embolism. Foramen ovale is a fissure-like channel that connects the left and right atrium. we know that the pressure of the left and right atrium is low in the cardiac cavity, and thrombus can be formed in the foramen ovale due to the influence of the flow and velocity of blood flow. this part of the thrombus may also lead to ischemic stroke; under conditions such as deep breathing and coughing, the unclosed foramen ovale opens, and tiny thrombus in the venous system enters the systemic circulation through the foramen ovale to cause cerebral embolism.

3. Treatment

A number of large clinical studies have been conducted on interventional occlusion of PFO in stroke patients with PFO. Previous studies have not shown the advantages of interventional occlusion. The long-term follow-up results of recently published studies show that interventional occlusion of PFO is superior to drug therapy in preventing recurrent stroke in stroke patients with PFO. There is still a lot of controversy about the treatment of PFO.

anticoagulation and antiplatelet medication: Equal effect

Homma S et al [5] studied the use of drug therapy (warfarin and aspirin) in patients with PFO or cryptogenic stroke, of which 98 participants were considered to have cryptogenic stroke or PFO. The results showed that there was no significant difference in stroke recurrence rates within 2 years between subjects taking warfarin and aspirin, which was 2 vs 42 (4.8%) vs 8/56 (14.3%) (HR 0.52, 95% CI 0.16-1.67).

NAVIGATE-ESUS [6] was an international, double-blinded, randomized phase III trial conducted at 459 centers in 31 countries that enrolled 7213 participants. The study rationale, design, participant features, and main results have been previously published, 6–8 including bleeding rates and the effects of treatment on major bleeding outcomes which randomized patients to aspirin, 100 mg daily, or rivaroxaban, 15 mg once daily and there was no significant difference in recurrent stroke risk comparing patients taking rivaroxaban with those taking aspirin, HR 0.54 (95% CI, 0.22–1.36). Major bleeding risk was likewise not significantly different, HR 2.05 (95% CI, 0.51–8.18).

The ESUs trial [7] randomized patients to aspirin, 100 mg daily, or dabigatran, 150 or 110 mg, twice daily. Overall, 680 / 5390 (12.6%) patients were found to have PFO, and there was no difference in the risk of recurrent stroke, HR 0.88 (95% CI, 0.45-1.71). There was no major bleeding risk in the PFO subgroup, on the whole, there was no difference between patients taking dabigatran and aspirin, with an RD of 0.5% (95% CI: - 0.4% to 1.3%).

4. PFO closure and medical therapy: Different opinions

The CLOSURE I study conducted by Furlan et al [8] is a multicenter, randomized controlled trial to compare the efficacy of interventional occlusion of PFO and drug therapy alone in the prevention of recurrent stroke in stroke patients with PFO. A total of 909 subjects were randomly divided into two groups: interventional occlusion group (n = 447) and drug treatment group (n = 462). The patients in the interventional occlusion group were treated with STARFlex occlude combined with antiplatelet therapy and the drug treatment group were treated with anticoagulation or antiplatelet therapy. During the follow-up for 2 years, there was no significant difference in the risk of recurrent stroke between the two groups (P = 0.79), and there was no significant difference in the risk of TIA between the two groups (P = 0.44).

The PC study conducted by Meier et al. [9] included 414 patients

under 60 years old with PFO complicated with stroke or TIA or peripheral thromboembolic events. They were randomly assigned to receive interventional occlusion with Amplatzer PFO occluder group and antithrombotic treatment group. The average follow-up of interventional occlusion group was 4.1 years, and that of drug treatment group was 4.0 years. There was no significant difference in the risk of stroke and TIA between the two groups. Compared with drug therapy, interventional occlusion therapy did not reduce the risk of stroke recurrence in patients with PFO complicated with stroke.

The RESPECT study conducted by Carroll et al [10] is to evaluate whether PFO occlusion is superior to drug therapy in the prevention of recurrent ischemic stroke in PFO patients with stroke. The trial included 980 patients with PFO. 499 patients in the interventional occlusion group were randomly assigned to receive antiplatelet therapy after interventional occlusion of PFO, and 481 patients in the drug treatment group were given antiplatelet therapy (74.8%) and anticoagulation therapy (25.2%). The mean follow-up was (2.6 ± 2.0) years. In the intention-to-treat analysis, recurrent stroke was reported in 9 of 499 (1.8%) participants assigned to device closure compared with 16 of 481 (3.3%) in the medical arm (rate difference -0.70% per year, 95% CI, -1.56% to 0.08% per year).

The CLOSE study conducted by Mas et al [11] mainly evaluated whether PFO occlusion was superior to drug therapy in stroke patients with PFO accompanied by atrial septal bulge or a large number of right-to-left shunts. The study included 663 patients with recent ischemic stroke complicated with PFO with atrial septal bulge or massive right-to-left shunt. They were randomly divided into interventional PFO group (n = 238) and drug treatment group (n = 235). The mean follow-up was (5.3 ± 2.0) years. The results showed that the incidence of stroke events in the interventional occlusion group was significantly lower than that in the antiplatelet group (P < 0.001). However, the incidence of atrial fibrillation and / or atrial flutter in the interventional occlusion group was higher than that in the antiplatelet group (P = 0.02). The final results show that PFO interventional occlusion can significantly reduce the stroke recurrence rate in recent stroke patients with PFO complicated with atrial septal bulge or a large number of right-to-left shunts.

The REDUCE study conducted by Søndergaard et al [12] is mainly used to evaluate whether PFO interventional occlusion in stroke patients with PFO is superior to drug therapy in the prevention of recurrent ischemic stroke events or new cerebral infarction. The trial included 664 patients with recent ischemic stroke complicated with PFO. 441 patients in PFO interventional occlusion group were randomly assigned to receive antiplatelet therapy after interventional occlusion of PFO. During the average follow-up of 3.2 years, the incidence of ischemic stroke in the interventional occlusion group was significantly lower than that in the drug treatment group (1.4% vs 5.4%, P = 0.002), and the incidence of new

cerebral infarction in the interventional occlusion group was lower than that in the drug treatment group (5.7% vs 11.3%, $P = 0.04$). The incidence of recurrent ischemic stroke events in the interventional occlusion group was significantly lower than that in the drug treatment group (1.3% vs 6.8%, $P = 0.005$). The results showed that in recent stroke patients with PFO, PFO interventional embolization therapy could significantly reduce the incidence of recurrent ischemic stroke events and new cerebral infarction compared with antiplatelet therapy alone.

4. Discussion

Patent foramen ovale and cryptogenic stroke are common diseases in the population. With the elaboration of evidence-based medicine evidence, in 2018, Canadian guidelines have been updated to block PFO as a secondary prevention strategy for patients with CS (evidence level A) [13]. In 2019, the latest report from JACC Magazine showed that the safety and effectiveness of PFO occlusion were further confirmed in 201 patients who were followed up for more than 10 years [14]. In the 2020 guidelines issued by the American Academy of Neurology [15], In patients being considered for PFO closure, clinicians should ensure that an appropriately thorough evaluation has been performed to rule out alternative mechanisms of stroke, as was performed in all positive PFO closure trials. Before undergoing PFO closure, patients should be assessed by a clinician with expertise in stroke to ensure that the PFO is the most plausible mechanism of stroke.

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