

CRYPTOGENIC STROKE (PFO SHOULD BE CLOSED)

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According to the epidemiological studies, a prevalence of 44% to 66% of patent foramen ovale (PFO) has been found in patients with cryptogenic stroke as compared with 27% in autopsy series of all-cause deaths. The higher prevalence of PFO in patients with cryptogenic stroke suggests that in some patients with cryptogenic stroke, the cause of stroke might be paradoxical thromboembolism (PTE).

Although the statistical association between PFO and stroke is clear, the causal relationship is not. In patients with cryptogenic stroke and PFO, PTE might not be the usual cause of stroke. Stroke occurs coincidentally with a pulmonary embolus (PE) or with visualised thrombus crossing the IAS. In these cases the pathogenesis of stroke is clearly paradoxical embolism. The association with large PFOs certainly suggests paradoxical embolism as the cause. Sometimes, the PFO is associated with an alternative pathology, such as asymptomatic cardiac arrhythmias. The septal defect acts as a donor site for thrombus formation. It is certainly plausible that relative homeostasis with a PFO tunnel could predispose to thrombosis. There is no definite answer from the available data; it may be a combination of more than one mechanism which underlies the association between PFO and cryptogenic stroke.

The appropriate medical management of stroke patients with a PFO has been ongoing for almost two decades. In a recent systematic review and meta-analysis of medical management of patients with PFO and with a history of cryptogenic ischemic stroke or transient ischemic attacks suggest that there was no superiority of different medical management strategies demonstrated. In parallel to research being conducted on medical interventions in stroke prevention in patients with a PFO, there have been series of studies devoted to physical closure of a PFO and elimination of RLS.

There is one multicentre randomized controlled trial (CLOSURE 1 [Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale]) recently reported. This was a randomized open-label trial on the effectiveness of PFO closure versus medical management in patients aged 18–60 with a PFO and a history of a cryptogenic cerebral event such as stroke or transient ischemic attack. The primary end point was composed of stroke, transient ischemic attack during 2 years' follow up, any cause of death during the first 30 days and death from neurological causes between 31 days and 2 years. In total, 909 patients were enrolled into this trial. The incidence of the primary end point was similar in both groups (5.5% in device closure and 6.8% in medically treated; adjusted hazard ratio 0.78; 95% CI: 0.45–1.35). The rates for stroke were 2.9 vs. 3.1% in device versus medically treated, and for transient ischemic attack, they were 3.1 versus 4.1%, respectively ($p = 0.44$). The CLOSURE 1 trial failed to demonstrate any significant difference in RNE with PFO closure compared with medical management.

On the contrary, several single-centre experiences indicated reduction in recurrent neurological events (RNE) after PFO closure. Briefly, data for RNE after percutaneous closure (39 studies with 8.185 patients) and medical therapy (19 studies with 2.142 patients) were recently published as an extensive review. Of these, 10 studies with 1.886 patients reported comparison of the 2 treatment modalities. The incidence of RNE/100 PY among the trans catheter closure was estimated as 0.76 (95% CI: 0.48 to 1.05) events as compared with 4.39 (95% CI: 3.20 to 5.59) events in the medical therapy arm. With comparative studies, there was a significantly reduced number of RNE among patients undergoing trans catheter closure as compared with those managed medically (RR: 0.25 [95% CI: 0.11 to 0.58]). Metaanalysis of the small number of comparative studies indicated that there might be a significant benefit in reduction of RNE with trans catheter closure in comparison with the medical therapy alone.

Finally, the benefit was found with observational studies but it was not able to prove in the CLOSURE 1 trial. There are several interesting points about the trial that are worth considering. The real-world selection of high-risk patients where PFO was more likely to be the cause of the stroke is likely to be a more beneficial strategy in successful prevention of RNE after trans catheter closure. In clinical practice when facing a young patient with recurrent ischemic stroke (i.e. after a second event) on medical treatment, with massive RLS, presence of ASA and lack of other risk factors despite in depth investigations, a decision for PFO closure can be considered as a rescue.