Cryptogenic stroke over 60 years of age: should patent foramen ovale be closed?

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Patent foramen ovale (PFO) is an anatomical communication between the left and the right atrium due to the lack of completed sealing of the fossa ovalis. Epidemiologic data, for the most part derived from young populations studies, suggested that PFO, allowing paradoxical embolization of thrombotic material from the venous to the arterial district, could play a significant role in the pathogenesis of cryptogenic ischemic cerebral events. Recently, three randomized studies in patients ≤60 years of age demonstrated the superiority of percutaneous closure of PFO over medical antithrombotic treatment. Several studies, on the other hand, indicated that also in older patients with cryptogenic cerebral ischemia, there was an higher prevalence of PFO in patients at low atherosclerosis and cardioembolic risk, and increased incidence of adverse cerebral events (mostly cryptogenic in patients treated medically, but likely due to a new cause in patients who had percutaneous closure of PFO). Advanced age is associated with more risk factors for deep vein thrombosis, and consequent paradoxical embolization through the PFO, so much so that careful consideration should be given to patients over the age of 60 years with cryptogenic stroke, as to not forgo the benefit of percutaneous closure of PFO, merely for anagraphic consideration. This consideration is particularly poignant in light of the more recent technical advances now available, such as direct percutaneous suture, mostly appealing for elderly patients, for its better tolerability and high safety both peri-procedural and during the follow-up, as well as the lack of necessity for antithrombotic treatment.

Introduction

The patent foramen ovale (PFO) is a congenital defect that determines an anatomical communication between the left atrium and the other right due to the failed closure of the oval fossa that normally occurs after birth with the fusion of septum primum and septum secundum. The persistence of PFO affects about one in four people but its prevalence is significantly greater in patients with cryptogenic stroke. This fact obtained essentially in young populations, suggested that PFO, allowing paradoxical embolization of thrombotic material from the venous district to the arterial system, could play a key role in the pathogenesis of cerebral ischemic syndromes for which there is no obvious cause. It is currently estimated that about a third of the 400,000 transient ischemic attacks and strokes that occur each year in western Europe are cryptogenic. The best therapeutic strategy for the prevention of cerebral ischemic recurrences has been the subject of numerous studies in the last 20 years. Recently, three randomized trials have demonstrated the superiority of percutaneous closure compared to antithrombotic medical therapy in the reduction of recurrent cerebral ischemic events in patients with a history of cryptogenic stroke attributable
to a PFO. In these studies, however, only patients of age less than or equal to 60 years were enrolled.

**Association between patent foramen ovale and cryptogenic stroke in patients over 60 years old**

In an influential meta-analysis of case-control studies published in 2000, the association between PFO and cryptogenic stroke was significant in patients younger than 55 years but not in older patients. However, the excessive heterogeneity among the studies included in this second group of patients significantly invalidated the reliability of the result.

In 2007, in an analysis of 503 consecutive patients with a history of stroke, the prevalence of PFO was significantly greater in patients with cryptogenic stroke than in patients with stroke due to other causes whether the age was lower (44% vs. 14%, \( P < 0.01 \)) or higher (28% against 12%, \( P < 0.001 \)) than 55 years. This study was markedly different from the previous ones in that all the subjects enrolled had undergone a transoesophageal echocardiogram for the diagnosis of PFO and were evaluated prospectively.

This finding was recently confirmed in a population-based analysis conducted in the Oxford Vascular Study in which consecutive patients with recent transient ischaemic attack or non-invalidating stroke were studied with transcranial Doppler, demonstrating a significantly higher right-to-left shunt prevalence in patients with cryptogenic cerebral ischaemia (36% vs. 21%, \( P < 0.001 \)). The clinical characteristics of the patients, very similar to those of the subjects enrolled in the studies on percutaneous PFO closure, constitute a distinctive and relevant aspect of this study. Furthermore, in an extrapolation of their results to the British population, the authors calculated that every year 8477 cryptogenic cerebral ischaemic events could occur, attributable to a significant right-to-left shunt, of which 70% in patients older than 60 years.

**Cryptogenic stroke risk in patients with patent foramen ovale and over 60 years**

In a different analysis of the Oxford Vascular Study, patients with recent cryptogenic stroke (average age 70 years) showed a significantly lower prevalence of single atherosclerotic risk factors. Consistently their overall number, the presence of symptomatic atherosclerosis in another arterial district, and the risk of experiencing an acute coronary event were lower compared to stroke patients due to large and small cerebral blood vessel disease. Similarly, patients with cryptogenic stroke had the lowest prevalence and lowest incidence of subclinical episodes of long-term paroxysmal atrial fibrillation, the lowest prevalence of cardiac abnormalities detectable in a standard echocardiogram and the lowest risk of systemic embolic events compared with patients with other types of stroke. Overall, these data indicate that patients with cryptogenic stroke have a low atherosclerotic and cardioembolic risk.

On the other hand, with age advancing some relevant factors, such as changes in endothelial and platelet function, comorbidity and reduced physical activity, increase the risk of thrombosis in the veins of the pelvis and lower limbs. Furthermore, in older patients, the diameter of the PFO is larger and the filling pressure of the right ventricle is greater. Thus, the higher probability of thrombotic material in the venous district and of haemodynamic conditions favouring a right-to-left shunt increase the risk of paradoxical embolism in elderly patients.

**Risk of recurrent events in patients with advanced age with patent foramen ovale and cryptogenic stroke**

In a retrospective analysis of the PICSS study (PFO In Cryptogenic Stroke Study), 250 patients treated with medical therapy were divided by age into three categories: <55 years, 55-64 years, 65 years or older. Of these patients, 98 (39%) had a PFO. Recurrent death and stroke have a significantly greater risk in patients aged 65 years and over (hazard ratio 3.21; 95% confidence interval 1.33-7.75; \( P = 0.01 \)) but not in the two younger patient’s groups (hazard ratio 0.21; 95% confidence interval 0.02-1.78; \( P = 0.15 \) in patients under 55 years and hazard ratio 0.72, 95% confidence interval 0.14-3.73; \( P = 0.70 \) in patients aged 55-64 years).

In a British study of 2555 patients with a mean age of 74 years and recent strokes, a large percentage of recurrences (63%) were cryptogenic. In turn, these data suggest that the exclusion of patients over 60 years may have affected the outcome of clinical trials comparing medical therapy with percutaneous PFO closure.

**Risk of recurrent events in patients of advanced age subjected to percutaneous patent foramen ovale closure**

Several series have been published of patients over 55 years of age undergoing percutaneous PFO closure with device implantation following a cryptogenic stroke. Table 1 summarizes the salient features. Studies differ in methodological rigour, presentation of data, and results. When available, the prevalence of atherosclerotic risk factors, in particular, systemic arterial hypertension, hypercholesterolaemia, diabetes mellitus, is significantly greater in patients aged over 50 years, while the percentage of residual shunt does not appear different between the two groups.

The first two published studies refer to American registries and do not demonstrate a significant difference in recurrent neurological events in patients older than 55 years. The next two European studies both show a markedly longer follow-up, and a significantly increased incidence of ischaemic neurological events in patients over 55 years. For the latter two studies the Kaplan-Meier curves begin to separate late suggesting an evolution of the general clinical picture and the intervention of a new cause in patients with new cerebral ischaemic event. This data appears in agreement with the demonstration, in patients
with PFO and cryptogenic stroke, of an identifiable cause other than paradoxical embolism in more than one-third of recurrent neurological events.\(^{14}\)

Finally, no study showed a different incidence of periprocedural complications between the two groups of patients following percutaneous closure of PFO with an implantable device.

**Current events and future developments in the treatment of patients with patent foramen ovale**

After a long debate in the scientific community on the best treatment of patients with PFO, in 2017, the results of three important randomized clinical studies were published—the extended follow-up of the RESPECT study, the REDUCE study and the CLOSE study—which demonstrate a reduction of ischaemic neurological events following percutaneous PFO closure with an implantable device compared to medical therapy with acetylsalicylic acid.\(^{15}\) On the other hand, the closure of the PFO by percutaneous suture with the NobleStitch EL system appears absolutely promising. This technology involves the use of two distinct catheters for the polypropylene suture of the septum secundum and of the septum primum and of a third catheter to guarantee a closure of the fossa ovalis implemented through the bending of the septum primum towards the right atrium so as to determine the coaptation with the septum secundum stabilized by suture fixation (Figure 1). The advantages of this approach include an increased patient comfort and a higher procedural safety due to the absence of transoesophageal echocardiographic guidance and the necessary sedation, the absence of a device implanted in the heart and of any foreign material in the left side of the interatrial septum, the predictable absence of complications typically attributable to the presence of the device and, in particular, the non-necessity of antithrombotic therapy.

The NobleStitch EL Italian Registry showed at an average follow-up of 206 ± 130 days the presence of a right-to-left shunt of Grade 0-1 in the vast majority of patients (89%) and no complication related to the suture of atrial septa were observed, with no episodes of atrial fibrillation.\(^{16}\)

**Conclusions**

Although the prevalence of clinical features associated with stroke from known causes increases with age, the same happens with factors favouring paradoxical embolism through a PFO. Furthermore, the inclusion of subjects aged <60 years in randomized clinical trials that have demonstrated the advantage of percutaneous PFO closure should not be a preclusion to the treatment of older patients who are at greater risk of recurrence of cerebral ischaemia. In a patient over 60 years, a careful evaluation of the temporal and topographical characteristics of the stroke, atherosclerotic risk factors, cardiac rhythm, inter-ventricular septum anatomy, lower limb veins, degree of autonomy, of co-morbidities and haemo-coagulative balance help to assess the relative risk of a cryptogenic stroke compared to an ischaemic event from other causes. Furthermore, the recent introduction in the clinical field of PFO closure by percutaneous suture appears particularly favourable for...
use in older patients for better tolerability and safety of the procedure.

**Conflict of interest:** none declared.

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