

# Association between atrial septal abnormalities (patent foramen ovale, atrial septal defect, interatrial septal aneurysm) and cryptogenic stroke in children

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## Abstract

Among cardiac diseases, those defined as cardio-embolic generate blood clots that, when traveling in the bloodstream, can partially or completely obstruct brain vessels thus causing a transient ischemic attack or a stroke. Patency of foramen ovale, atrial septal defect, and interatrial septal aneurysm are well known cardiac anomalies whose clinical significance is still under debate. Usually diagnosed by echocardiography, they are often associated with otherwise unexplained (cryptogenic) stroke at a young age, including paediatric patients.

Despite this widely reported in literature link, defining the exact pathogenetic mechanism by whom they are associated with systemic thromboembolism is difficult.

In this practical review, we try to clarify their pathogenetic role in inducing cerebral ischemia. Related treatment options are discussed as well.

## Keywords

Stroke, transient ischaemic attack, patent foramen ovale, atrial septal aneurysm, interatrial aneurysm.

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## Introduction

Stroke is quite rare in paediatric age, although associated with significant morbidity and mortality. It is defined as a neurological injury caused by the occlusion (ischemic stroke) and/or rupture (haemorrhagic stroke) of brain blood vessels. Recent studies showed that the incidence of stroke is on a downward trend among the elderly and conversely on an upward trend in the young population [1]. Ischemic stroke accounts for about 50% of all strokes in children, whilst in adults about 80-85% of all strokes are of ischemic origin [2, 3]. Not only, but children have a larger number of risk factors for ischemic stroke which differ significantly from adults as well. Regarding its mortality and morbidity, around 10-25% of children with stroke will pass away, up to 25% of them will have a recurrence, and up to 66% will suffer from persistent neurological deficits or develop epileptic attacks, learning disabilities and developmental delays [4-6].

The reported incidence of combined ischemic and haemorrhagic stroke ranges from 1.2 to 13 cases per 100,000 subjects under the age of 18 [7-15].

In addition, paediatric stroke is often undiagnosed, misdiagnosed or delayed. This may be due to a lot of factors, including low level of suspicion by clinicians or patients who present with subtle symptoms mimicking other diseases [16]. Brain imaging (CT or MRI brain scan) is often needed before confirming diagnosis [17]. However, the reported incidence of paediatric stroke is more than doubled compared to the previous decade [18]. This is likely to be linked with a combination of raised survival in children with risk factors for ischemic stroke (such as congenital

heart disease, sickle cell disease, and cancer), and increased awareness [18-27]. Aetiologies like high blood pressure, hypercholesterolemia and atherosclerosis, diabetes, smoking habit, arrhythmias, infective endocarditis, systemic diseases are decidedly less frequent than in adults [28-40].

## Interatrial septum embryology

During foetal life, at week fourth of gestation, the first stage of interatrial septum formation is the development of a membranous septum called septum primum, which comes off the posterior roof of the common atrium. This septum grows in the primary atrial cavity toward the endocardial cushions and gradually separates the common atrium into a right and a left atrium. Before the septum primum reaches the intermediate septum, derived from the endocardial cushions, the opening that remains is called ostium primum. As the septum primum grows, ostium primum gradually reduces and, when the margin of the septum primum reaches the intermediate septum, it becomes obliterated. Meanwhile, due to a process of programmed cells death in the septum primum, small openings appear and converge in a hole between the two atria, the so-called ostium secundum.

A second proliferation made up of muscle appears in the ventro-cranial wall of the atrium, to the right of the septum primum. It is called septum secundum. It grows parallel to the septum primum but does not reach the intermediate septum.

The opening that persists between the free edge of the septum secundum and the ostium secundum is known as foramen ovale.

The upper portion of the septum primum merges with the septum secundum while the remaining portion becomes a valve-like structure for the oval foramen. The latter is placed at the posterior extremity of the septum in direction of the outlet of the caudal vena cava.

During foetal life the two atria are then separated by two parallel septa and nevertheless communicate through their respective holes: the ostium secundum of the septum primum and the oval hole of the septum secundum [41].

## Patent foramen ovale and stroke

A foramen ovale is an anatomical structure which allows communication between the two

atria. While an atrial septal defect is a hole in the interatrial septum, foramen ovale is a left-to-right tunnel. During foetal circulation, it allows the oxygenated blood coming from the placenta through the inferior vena cava to cross over the interatrial septum and reach the left side of the heart. A well-developed Eustachian valve in the right atrium plays a pivotal role in directing the blood from the inferior vena cava to the foramen ovale and so that in the left atrium [42].

After birth, respiration lowers pulmonary vascular resistances, thus increasing pulmonary blood flow as well as pulmonary venous return into the left atrium which, in turn, raises left atrial pressure, thus forcing the septum primum against the septum secundum. A so-called “functional” closure of foramen ovale is reached. As times goes by, the two septa become fused to each other (“anatomical” closure of foramen ovale). This process does not occur in about 25-30% of the general population, thus leaving a patent foramen ovale as shown by autopsy findings and echocardiographic reports [43, 44].

Even if a negligible left-to-right blood shunt can occur through a patent foramen ovale, the latter mainly acts as a flap-like unidirectional valve. However, any increase in right atrial pressure can facilitate an inversion of the interatrial shunt (from left-to-right to right-to-left. It is called paradoxical embolism) [45]. This promotes small blood clots formation, which may travel from the left side of the heart to the brain and cause an ischaemic stroke [45-48].

Regarding diagnosis of patency of foramen ovale, transthoracic echocardiography, without saline injection, cannot reliably diagnose it and should not be used for this purpose. Both transcranial Doppler and transthoracic echocardiography, when performed in association with injection of an agitated saline solution in a peripheral vein, can make the diagnosis of a right-to-left shunt with a high sensibility and specificity (97% and 93% for transcranial Doppler; 91% and 93% for transthoracic echocardiography) [49, 50]. Performing a Valsalva maneuver is part of both examinations with the aim of increasing venous return to the right atrium and eliciting a right-to-left shunt in the setting of a patent foramen ovale. Whilst transcranial Doppler can appropriately quantify the magnitude of the shunt by means of the high intensity signals recorded at the level of the medial cerebral artery, it cannot identify the site of that shunt, which rarely may be due to other

causes, such as pulmonary fistulas. Even if by using transthoracic echocardiography the site of shunting may be identified at times, only transoesophageal echocardiography is capable of confirming that patency of foramen ovale is the real source of the shunt. Not only, but it allows also to describe its anatomical features, which are of relevance when planning its interventional closure [51].

Furthermore, in patients with a history of unexplained ischemic stroke, any less common possible different cardioembolic source (such as atrial myxoma, left atrial appendage thrombosis, left ventricular thrombus or papillary fibroelastomas) should be looked for [52].

In literature, patency of foramen ovale was often associated with a few conditions other than stroke, such as migraine with aura, transient global amnesia, platypnea-orthodeoxia syndrome, obstructive sleep apnoea syndrome, and decompression illness in scuba divers. Nonetheless, given the high prevalence of patent foramen ovale in the general population, its real correlation with these conditions is far from being confirmed at all [53].

As to the possible link with migraine, previous case-control studies showed a higher prevalence (from 40% to 60%) of patency of foramen ovale in subjects affected by migraine with aura than in the general population as well as a higher prevalence of migraine with aura in subjects with a patent foramen ovale (from 13% to 50%) [54, 55].

Many retrospective studies reported a significant improvement of migraine severity after patent foramen ovale closure [56]. However, the randomized MIST trial, comparing patent foramen ovale interventional closure to medical therapy in that setting, failed to show any substantial improvement in symptoms after closure. Not only, but 6.8% of those in the device group suffered from complications related to the interventional procedure [57]. Finally, while the presence of white matter lesions at brain MRI is frequently encountered in patients suffering from migraine with aura, there is no correlation between the white matter lesion load and the amount of right-to-left shunt at patent foramen ovale site [58].

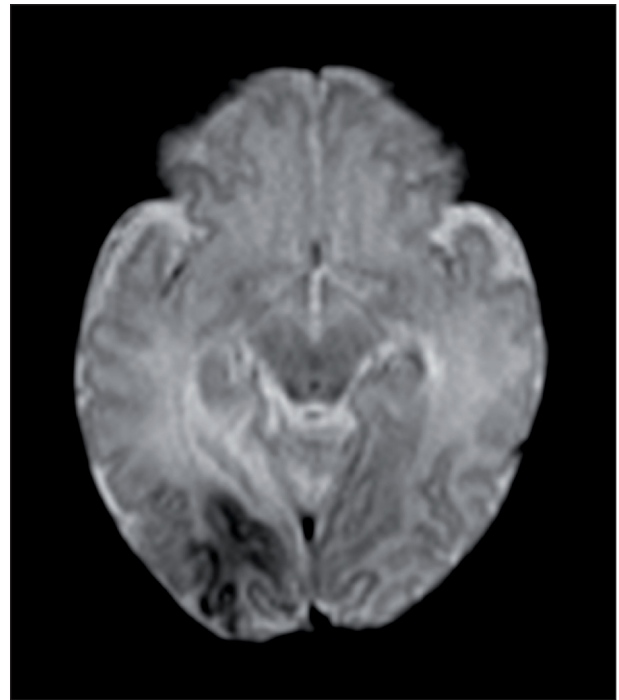
Overall, there is no evidence to support patent foramen ovale closure to relieve symptoms of migraine. Furthermore, migraine has long been considered a risk factor for ischaemic stroke, due to the concomitant presence of endothelial abnormalities, reduction of cerebral blood flow, and platelet hyperaggregability. However, as the

latest SPREAD guidelines show, this relationship was completely reversed and revised [59].

Cryptogenic stroke is defined as an ischaemic stroke with no identifiable cause after a full diagnostic work-up. It accounts for up to 40% of ischemic strokes in children and adolescents. Transient ischemic attacks of unexplained origin are possible as well. Prevalence of patency of foramen ovale was shown to be (even six-time) higher in patients younger than 55 who suffered from a cryptogenic stroke than in subjects with a known cause, as showed in a metanalysis of 28 studies, thus strongly suggesting an association between the two [60]. The hypothesized mechanism accounting for this association is paradoxical embolism. The latter is defined as a clot entering the systemic circulation through a patent foramen ovale. The occasional finding in children with a stroke of a thrombus crossing a patent foramen ovale constitutes a persuasive argument of paradoxical embolism being the underlying cause of the disease, but unfortunately it is an exception rather than the general rule [61, 62].

Detecting the patency of foramen ovale is not the most difficult thing in the diagnostic work-up of cryptogenic stroke. In fact, establishing the probability that it is the real cause of stroke and not only an incidental finding plays a pivotal role in decision-making process. A personalized or “tailored” approach is needed [63]. The RoPE (Risk of Paradoxical Embolism) score helps to identify patent foramen ovale-related brain accidents in patients with cryptogenic stroke and is a very useful tool in patients with no other compelling cause for that [64]. Included in the scoring system are patient’s age (the younger the age, the higher the score), absence of hypertension/diabetes/smoking habit (one point each), no previous stroke/transient ischaemic attack (one point) and features of cerebral lesion at brain imaging (i.e. one point for superficial [cortical] lesion. See **Fig. 1**). The final score ranges from 0 to 10. Those with the higher scores are more likely to have suffered from a stroke caused by a patency of foramen ovale [64].

In an attempt to further refine these subjects, a few anatomical interatrial features were identified as leading to an increase in the likelihood of paradoxical embolism or in the risk of recurrences, such as a large and/or long foramen ovale tunnel (> 4 mm in width and > 10 mm in length), the presence of an atrial septal aneurysm or a redundant Eustachian valve (> 10 mm in length) in the right atrium [65-76]. However conflicting evidence as to their role



**Figure 1.** CT brain (diffusion-weighted imaging) showing a cortical/subcortical acute ischaemic lesion in the postero-medial territory of the right cerebral hemisphere. Laminar damage is evident as well. The patient was aged 3 months.

was reported, so that overall their predictive value seems to be quite low [71, 72]. Again, right-to-left shunt severity at transcranial Color Doppler is positively linked with a higher RoPE score, thus indicating that this technique for shunt grading identifies patients more likely to have pathogenic rather than incidental foramen ovale [73]. Additional predisposing factors for paradoxical embolism are a recent prolonged flight, Valsalva maneuver preceding the neurological symptoms and inherited coagulation disorders [74, 75].

### Atrial septal defect and stroke

It is defined as an open communication between the two atria. Atrial septal defects vary in size and locations. However, the vast majority of them are ostium secundum type, i.e. in the middle of the interatrial septum, due to a deficiency in the septum primum. Recently it was demonstrated that cryptogenic stroke can occur even in patients with small or insignificant atrial septal defects, because of left-to-right paradoxical embolism due to an increase in right atrial pressure [76]. The latter is relatively common during pregnancy, so that all atrial septal defects regardless of size should be considered for closure before that [77]. Atrial

septal defects are associated with a paradoxical embolism in up to 14% of patients [78].

### Atrial septal aneurysm and stroke

Atrial septal hypermobility seems to be linked with a higher risk of cryptogenic stroke in those with a RoPE score major than 6 [79].

Atrial septal aneurysm is a thinning of interatrial septum and often associated with a patent foramen ovale. Other times it is multi fenestrated. It tends to move from one side of the atria to the other during systole (like a small flag-waving sail). Due to echocardiography and its rapid evolution, atrial septal aneurysm is now a well-known cardiac anomaly [80].

Morphologically, the atrial septal aneurysm is described as a thinned wall consisting of connective tissue bounded on both surfaces by endothelial cells. Autopsy studies showed that an aneurysmal septum is thinner (0.4-0.8 mm) than a normal septum (2 mm), muscle cells are absent or degenerated and, finally, there are more fat cells and fewer collagen fibres [81].

As it may be difficult to distinguish between a slightly redundant (“floppy”) septum and a true aneurysm, in the Eighties of the last century a clear definition was established by Hanley et al. [82], namely:

- protrusion or “bulging” of the interatrial septum or a part of that > 15 mm, beyond the midline that identifies the plane of the septum;
- phasic excursion of the interatrial septum, during the respiratory cycle, with an overall sum of the excursion > 15 mm;
- base of the aneurysm portion > 15 mm.

These criteria were subsequently modified by other authors and the actual classification is that proposed by Olivares-Reyes et al. [83], which subdivides this anomaly into five types:

- type 1R: with protrusion towards the right atrium;
- type 2L: with protrusion towards the left atrium;
- type 3RL: with maximum excursion towards the right atrium and minor excursion towards the left atrium;
- type 4LR: with maximum excursion towards the left atrium and minor excursion towards the right atrium;
- type 5: the excursion is bidirectional with similar excursions toward both atria.

The prevalence of the aneurysm of the interatrial septum varies a lot depending on three conditions:

the technique of detection (transthoracic vs transoesophageal echo), the studied population and the used definition.

Owing to the anatomic location of atria, which are posterior, they are better visualised by means of transoesophageal echocardiography. Nowadays however, the possibility of missed diagnosis of this defect (false negatives) using transthoracic echo was reduced to a bare minimum thanks to the giant steps forward taken by echocardiography [84]. When using the restrictive definition introduced by Olivares-Reyes, the prevalence of interatrial septum aneurysm in the general population ranges from 0.2% to 3.2%. This percentage increases markedly in populations affected by cryptogenic stroke, ranging from 16.5% to 32% [84, 85]. When focusing on specific populations, such as the preterm born and/or with those born with low birth weight, the prevalence is about 30% [86]. This is because of the presence of an acquired interatrial septal aneurysm, whose appearance is related to the marked difference in pressure between the two atria, owing to a long-lasting patency of the ductus arteriosus and/or presence of severe respiratory distress at birth [87].

Regarding the link between paradoxical embolism and interatrial septal aneurysm, traditional Hanley et al.’s hypothesis suggested that extremely hypermobile aneurysms may stretch the atria, thus leading to the development of paroxysmal atrial fibrillation and increasing the risk of embolism [82, 88]. A different hypothesis is related to the formation “*in loco*” of small clots able to be lodged in the aneurysmal sac (blood stasis) [87].

The link between cerebral ischemia and interatrial aneurysm was, for the first time, suggested by Belkin and Kisslo in 1990 with a retrospective study and then confirmed by various multicentric studies [89]. In 1991, thanks to Pearson et al.’s work, the first case-control study was published, which showed a higher prevalence of interatrial aneurysm in patients with previous strokes than in their healthy peers [90]. Also in 1999, with the SPARC (Stroke Prevention: Assessment of Risk in a Community) study, a greater prevalence of interatrial aneurysm was confirmed in patients with ischemic strokes compared to the healthy controls, thus demonstrating that in 6% of patients there was no source of cerebral embolism rather than that [91].

However, if we consider paradoxical embolism as the pathogenetic mechanism of brain ischaemia, an isolated interatrial aneurysm itself is unlikely

to be able to induce a cryptogenic stroke. It needs to be associated with a patent foramen ovale or be multi fenestrated to increase the probability of right-to-left shunting, thus favouring the travel across it of a small clot.

### Therapeutic options

Numerous literature reports support the hypothesis that foramen ovale patency, most of all when associated with other atrial septal abnormalities such as an interatrial septal aneurysm and/or blood hypercoagulable state, is related to an increased risk of paradoxical embolism, whose most harmful consequence is cryptogenic stroke [92, 93].

However, due to a lack of randomized controlled trials in children and adolescents with stroke, the best treatment approach in secondary prevention (drugs or interventional closure to prevent recurrences from happening) is still far to be universally accepted [94]. Not only, but drug metabolism in children is markedly different than in adults and antiaggregant therapy at that age has not been studied enough. Thromboembolic events in childhood are not as common as they are in adults and related aetiologies are different, so that management studies are a challenge, and recommendations for antithrombotic therapy are mainly extrapolated from those for adults [95]. In addition to antiplatelet medication, also heparinization, intravenous thrombolysis and endovascular thrombectomy are potentially effective therapeutic options [96].

According to current Guidelines, clinicians may offer percutaneous closure of foramen ovale in rare circumstances, such as recurrent strokes despite optimal medical therapy with no other mechanism identified (American Academy of Neurology, 2016) or deep venous thrombosis at high risk of recurrence (American Heart Association/American Stroke Association, 2014) [97]. These suggestions are based on the analysis of randomized controlled trials CLOSURE I, PC, and RESPECT, which investigated efficiency and safety of percutaneous patent foramen ovale closure in comparison to medical therapy (Aspirin®) alone [98-100].

As to CLOSURE I and PC trials, in patients with cryptogenic stroke or transient ischaemic attack who had a patent foramen ovale, closure with a device did not offer a benefit greater than medical therapy alone in preventing recurrence of cerebral thromboembolic events or death. In

addition, a higher incidence of new onset atrial fibrillation and peri-procedural complications was noted with interventional closure [98, 99]. The RESPECT trial showed similar findings. Only in younger patients with a significant transatrial left-to-right shunt and/or an interatrial septal aneurysm, interventional therapy was superior to antiaggregant therapy [100].

Conversely, a number of up-to-date meta-analyses and reviews showed opposite outcomes, i.e. a decreased incidence of cerebrovascular events in those treated percutaneously. This was after including two more recently conducted trials (CLOSE and REDUCE), with more stiff inclusion criteria [101-104]. In the Italian registry IPSYS (Italian Project on Stroke in Young Adults) closure provided a benefit in patients younger than 37 years and in those with a substantial right-to-left shunt size [105]. This beneficial effect was even more evident when foramen ovale closure was combined with antiplatelet therapy versus antiplatelet therapy alone [106].

In summary, patent foramen ovale can be closed in terms of secondary prevention after a stroke or transient ischemic attack in appropriately selected patients, though the effectiveness of this strategy is still under debate. The ideal patients are very young subjects with no other risk factors and who have a moderate-to-severe right-to-left shunt through the interatrial septum. They show benefits with respect to recurrent strokes. Their long-term prognosis is strongly dependent on establishing a correct and prompt diagnosis. An appropriate counselling is needed to obtain patients' informed consent before the procedure is done [107]. Efficiency of percutaneous closure seems to be influenced by the type of implanted device as well. Additional studies are mandatory to evaluate the impact of higher incidence of atrial fibrillation seen with the patent foramen ovale closure device on long-term mortality and stroke rates [108-110].

### Declaration of interest

The Authors declare that there is no conflict of interest.

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