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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Efficiency of transcatheter patent foramen ovale closure in children after paradoxical embolism events

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Abstract

Background and aim: Patent foramen ovale (PFO) may result in a cerebrovascular event — a presumed paradoxical embolism (PE). However, the presence of this phenomenon among paediatric patients was rarely evaluated. Transcatheter PFO closure was considered to be a method of treatment in such patients.

Methods: For evaluation clinical data and long-term outcome, we reviewed records of patients below 18 years of age, with history of cerebrovascular event related to PE, who underwent procedure of percutaneous PFO closure in years 1999–2014 in our department.

Results: Among 230 patients with cerebrovascular events who had PFO closed percutaneously, seven children (aged 12––16 years, five male) were selected. Indications for closure were cryptogenic stroke in two patients and transient ischaemic attack (TIA) in five patients. Diagnosis of PFO was established by transthoracic echocardiography, with right-to-left shunt (RLS) through PFO confirmed by transoesophageal echocardiography. Contrast transcranial Doppler (c-TCD) was performed preprocedurally in four patients, revealing significant RLS. For percutaneous closure of PFO different occluders (Starflex, Amplatzer PFO devices, Cardio-O-Fix) were used. Closure was successfully completed in all patients and no procedure-related complications were observed. Postprocedural c-TCD six months after closure revealed no significant RLS. During follow-up (3 to 10 years) one patient had an episode of recurrent TIA; however, in this patient paroxysmal atrial fibrillation was found during the follow-up period.

Conclusions: Cerebral embolism due to PFO is uncommon in children. Transcatheter PFO closure in this group of patients is a safe and effective procedure. C-TCD is plausible technique for detection RLS and monitoring PFO closure efficacy in this group of patients.

Key words: cerebrovascular event, paradoxical embolism, patent foramen ovale, transcatheter closure

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INTRODUCTION

Patent foramen ovale (PFO) is present in about 25–30% of the general population [1]. Not being assessed as a heart defect, but as a physiological variant, it is suspected to be the cause of cerebrovascular ischaemic events including cryptogenic stroke (CS) and transient ischaemic attack (TIA) in paradoxical embolism (PE) pathomechanism [2]. There is still an open discussion regarding the management of this group of patients and the role of transcatheter closure of PFO in patients with a history of cryptogenic cerebral events. Results of three randomised control trials did not confirm superior efficacy of percutaneous PFO closure compared to medical treatment, including antiplatelets and oral anticoagulants [3–5]. However, these data are restricted to adult patients because they excluded patients below 18 years of age. As cryptogenic cerebral events can also occur in children, there is an urgent need for data related to these patients. The subject of this publication was analysis of clinical data and long-term outcomes of paediatric patients with cerebral events of presumed PE, who underwent transcatheter PFO closure.

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METHODS

Between 1999 and 2014, 230 patients with PFO and PE event were treated percutaneously in our department. Among them seven children (age < 18 years) were selected, treated in the years 2001–2011; there were five boys. Age at qualifying PE event ranged between 10 and 15 years with an average of 13.5 years, and the time from event to PFO closure was between three months and three years with an average of five months. Age of implantation ranged between 12 and 16 years with an average of 14 years. Indications for closure were CS, confirmed with magnetic resonance (MR) and computed tomography (CT), in two patients and TIA in five patients. All TIA patients had neuroimaging: four patients had MR, and three patients had CT, revealing no cerebrovascular lesions. Carotid stenosis and atrial fibrillation (AF) were excluded in all children (in one patient intraventricular conduction disturbances occurred), as well as hypercoagulable states (protein C and protein S deficiency, antithrombin III, ANA, lupus anticoagulants, anticardiolipin antibodies, history of peripheral thrombosis). Patients with only migraine in anamnesis were not qualified to percutaneous closure.

Contrast transcranial Doppler (c-TCD), being a routine procedure in all patients with suspicion of PFO in the Paediatric Cardiology Department since 2007, was performed before closure in four patients treated afterwards, monitoring middle cerebral arteries bilaterally, in spontaneous breathing, and during Valsalva manoeuvre. Contrast medium (9 mL of saline, 1 mL of air, agitated) was given via the antecubital vain. Results were assessed in a 0–3 scale (0 — no shunt, 1 — number of microembolic signals [MES] < 10, 2 — more than 10 MES but countable, 3 — uncountable, "embolic shower"), where 2nd and 3rd degree was considered to be a significant shunt. In all examined patients MES was registered after Valsalva manoeuvre (there were no spontaneous right-to-left-shunts [RLS]) and were significant (Table 1).

Transthoracic echocardiography (TTE) revealed PFO in five patients (two patients with comorbidity of septal aneurysm), including all three patients in whom preprocedural c-TCD was not performed. The diagnosis of PFO was confirmed in all patients during cardiac catheterisation with simultaneous transoesophageal echocardiography (TEE). All patients underwent TEE with saline contrast administration during the Valsalva manoeuvre before closure (all RLS type shunts), which was done under general anaesthesia, with antibiotic prophylaxis (cefazolin 100 mg/kg body weight administered intravenously) and heparin (100 IU/kg body weight), all performed by femoral vein approach. PFO canal lengths were 7–20 mm. Devices: Amplatzer APFO in four patients (18, 25, 25, 25 mm), Starflex in two patients (23, 28 mm), and Cardio-O-Fix PFO in one patient (18 mm) were successfully implanted in all patients. The duration of procedure ranged 10–50 min (average 29 min), including between 1 min and 11 min (average 4 min) fluoroscopy.

Cefazolin for three days in all patients, aspirin (150––325 mg) for six months in six patients, combined, in two of these patients, with clopidogrel (75 mg) for three months, and acenocoumarol (INR 2.5–3.5) for six months in one patient, were administered. All patients were followed up by TTE twice before leaving the ward and 1, 3, 6, and 12 months ambulatory after the procedure. C-TCD was performed six months after implantation in all but one patient (in patient no. 2 and no. 3 examinations were performed by the author [M.W.] in the Neurology Department because c-TCD was not available yet in the Paediatric Cardiology Department). The follow-up range (six patients) was 3–10 years (average 6.3 years).

Table 1. Clinical data and follow-up of patients

	Date of procedure	Age at implantation years/sex	Indication	TEE before closure	c-TCD before closure[1] [shunt degree]	Device	c-TCD after closure [shunt degree]	Follow-up time [years]	Follow-up
1	10.2001	13/male	TIA	+	/	Starflex 23	/[2]	/	/
2	08.2004	14/male	TIA	+	/	Starflex 28	0	10	No symptoms
3	06.2006	16/female	2 TIAs	+	/	Amplatzer PFO 18	1	8	No symptoms
4	10.2007	15/male	3 TIAs	+	3	Amplatzer PFO 25	0	7	TIA, AF
5	04.2008	12/male	TIA	+	2	Amplatzer PFO 25	0	6	Headaches
6	03.2010	15/female	CS	+	3	Amplatzer PFO 25	0	4	No symptoms
7	02.2011	14/male	CS	+	3	Cardio-O-Fix PFO 18	0	3	No symptoms

[1]Contrast transcranial Doppler (c-TCD) available from 2007; [2]Patient lost from follow-up; AF — atrial fibrillation; CS — cryptogenic stroke; TIA — transient ischaemic attack; TEE — transoesophageal echocardiography

RESULTS

The procedure was successfully completed in all patients, and no procedure-related complications were observed during hospitalisation (i.e. arrhythmias, vascular injury, or device embolisation). Control TEE during the procedure confirmed the correct position of the device.

In all patients, except one lost for follow-up, control c-TCD study was conducted six months after implantation with no significant shunt — in five patients no MES and in one patient two MES were registered.

In long-term observation one recurrent embolic event (EE) occurred. One month after Amplatzer APFO 25 implantation sight disturbances and muscle weakness of the left upper limb, lasting for 30 min (TIA) appeared in one patient. This incident was similar to the previous three TIAs. After the recurrent EE a TCD study was conducted, but the result, unlike the first one, was negative, and it was the same after six months. In this patient paroxysmal AF appeared during seven years of follow-up, despite the fact that no arrhythmias were found before PFO closure. AF appeared only once, and the sinus rhythm returned after amiodarone treatment.

Another patient continued to have headaches as he previously had before cerebral EE and Amplatzer APFO 25 implantation. Also in this case control c-TCD after six months was negative. In a six-year-long observation no shunt between atria was revealed. The remaining four patients revealed no symptoms.

All patients returned to normal daily activity, not excluding sport from their life. All of them consider themselves as healthy.

DISCUSSION

PFO is thought to be present in about 25–30% of the adult population. It is suspected to be the cause of ischaemic cerebrovascular events, mainly in PE pathomechanism, although susceptibility to atrial arrhythmias in these patients is also considered [6]. In patients with cryptogenic stroke, PFO (also coexisting with atrial septal aneurysm) is significantly more common compared to the general population [7]. However, the recurrence of cerebrovascular events in this group of stroke patients, assessed in prospective studies, was comparable to the population of stroke patients with known cause [8].

Also, therapeutic management in patients with a history of CS or TIA and the presence of PFO remains unclear. Data from observational studies conducted before 2012 strongly favour percutaneous PFO closure [9]. However, the results of three randomised control studies (RCT) do not confirm the superiority of invasive procedures compared to medical treatment, including antiplatelets or oral anticoagulants [3–5], and numerous meta-analyses of RCTs are also inconclusive [10–12].

There is a shortage of data regarding the implication of PFO in the child population [13, 14]. Ischaemic cerebrovascular events are relatively rare in this group of patients, but they are increasingly recognised [15, 16], resulting in disability and mortality. Paradoxical embolism across PFO was suggested as a possible aetiology of such events [17, 18]. Also, relation to prothrombotic disorders is raised in PFO patients with cerebral EE. Furthermore, recurrence of stroke is estimated in this age group at 25–30% [19, 20].

In our study only seven children were selected from 230 patients treated percutaneously, which represents only 3%. Two children had CS and in five TIA was recognised. All patients had neuroimaging: six patients had MR; moreover, five patients had CT. Vascular risk factors, including hypercoagulable states, were excluded in all children.

TEE remains a "gold standard" in the evaluation PFO. However, in children this procedure is not easy to perform compared to adults due to poor cooperation, and as a consequence general anaesthesia is usually required. Because of thinner thoracic wall, less invasive examinations like TTE are often sufficient for the evaluation of interatrial septum. All of our children had both TTE and TEE; TTE was revealed PFO in five patients, TEE in all of them.

C-TCD with Valsalva manoeuvre is a sensitive method for PFO detection, comparable to TEE [21, 22]. It allows also quantification of the degree of RLS by MES number, where > 10 MES is considered to be significant [22]. C-TCD is a minimally invasive procedure, harmless to children, except for getting vein access, and not requiring general anaesthesia or even pharmacological sedation. As the Valsalva manoeuvre is easy to learn and conduct in such circumstances, c-TCD seems to be particularly suitable for children, even as young as five years old [13]. A weakness of this method can be positive MES detection due to RLS different than PFO, i.e. pulmonary anastomosis. In our patients c-TCD was conducted in four patients before the procedure — all with significant number of MES, and in six patients after implantation — confirming lack or insignificant (one patient) degree of shunt after closure.

PFO closure is performed only exceptionally in children [18]. Benedik et al. [14] underline the lack of data regarding PFO closure in such young patients. In RCTs only patients over 18 years old were included [3–5]. According to another publication by Benedik et al. [23], transcatheter PFO closure in children is a relatively safe and effective procedure, which also makes it possible to discontinue long-lasting antithrombotic treatment, which is usually hard to maintain because of poor compliance and possible side effects. In our study the procedure was successfully completed in all patients, and no procedure-related complications were observed during hospitalisation. In all children, except one lost from follow-up, antiplatelets or Coumadin were withdrawn six months after the procedure.

One recurrent ischaemic episode was observed in a patient after Amplatzer APFO implantation; however, paroxysmal AF was noticed in this patient in the follow-up period. Although AF is a rare cardiac cause of stroke in children, in opposition to congenital heart lesions or valvular diseases [24],

its presence is associated with high risk of stroke, and both increased mortality and stroke recurrence [25].

PFO closure in children with cerebral PE event is still an off-label procedure because the protocol of qualification to either invasive or medical treatment of PFO has not been established. Three another randomised trials: REDUCE, CLOSE, and DEFENCE-PRO evaluating the safety and efficacy of transcatheter PFO closure versus medical therapy in reducing the risk of recurrent stroke in such patients are being performed at the time of writing, but only patients over 16 years of age are included. RCT among paediatric patients is strongly required, but the potential long time of enrolment and low number of recurrent events limit the prospects for receiving results within the next few years.

Limitations of the study

The retrospective design of our study, small group of patients, majority of children with history of TIA, being more subjective phenomenon than patients with completed CS, and not performing TCD in all of the patients before PFO closure are limitations of this study.

CONCLUSIONS

Although cerebral ischaemic events are rare in children, when they occur they may lead to permanent disability and require long-term medical therapy for prevention of recurrence. At least in some cases, which remain cryptogenic despite broad diagnostic management, PE through PFO may be a cause of event. Transcatheter PFO closure, being a safe and effective procedure, is a reasonable therapeutic option, but precise selection of patients and standardisation of qualification protocol is required. C-TCD is a plausible technique for detection RLS and monitoring PFO closure efficacy, especially in this group of patients.

Conflict of interest: *none declared*

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Skuteczność przezskórnego zamknięcia przetrwałego otworu owalnego u dzieci z wywiadem zatorowości paradoksalnej

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Streszczenie

Wstęp i cel: Przetrwały otwór owalny (PFO) może być przyczyną epizodów naczyniowych mózgu drogą zatorowości paradoksalnej (PE). Jednak ocena tego zjawiska wśród dzieci rzadko jest przedmiotem badań. Jedną z metod leczenia tych chorych jest przezskórne zamknięcie PFO.

Metody: Przeanalizowano dokumentację chorych poniżej 18. rż. z wywiadem epizodu naczyniowego mózgu przypisywanego PE, poddanych zabiegowi przezskórnego zamknięcia PFO w latach 1999–2014 w ośrodku, w którym pracują autorzy niniejszej pracy, oceniając dane kliniczne i okres obserwacji po leczeniu.

Wyniki: Wśród 230 chorych z wywiadem incydentów naczyniowych mózgu, u których wykonano zabieg przezskórnego zamknięcia PFO, było siedmioro dzieci (wiek 12–16 lat, 5 chłopców). Wskazaniem do zabiegu u 2 chorych był kryptogenny udar mózgu, a u 5 pacjentów przemijające niedokrwienie mózgu (TIA). Rozpoznanie PFO ustalono na podstawie przezklatkowej echokardiografii, z potwierdzeniem obecności przecieku prawo-lewego metodą echokardiografii przezprzełykowej. Kontrastową ultrasonografię przezczaszkową wykonano przed zabiegiem u 4 chorych, potwierdzając obecność istotnego przecieku. Do zamknięcia PFO wykorzystano różne okludery (Starflex, Amplatzer PFO, Cardio-O-Fix). U wszystkich pacjentów zabieg był skuteczny, nie zaobserwowano występowania powikłań. Kontrastowa ultrasonografia przezczaszkowa wykonana 6 miesięcy po zabiegu nie ujawniła obecności przecieku u żadnego chorego. W okresie obserwacji (od 3 do 10 lat) u 1 chorego wystąpił epizod TIA, jednak u tego pacjenta stwierdzono napadowe migotanie przedsionków.

Wnioski: Zatorowość mózgowa drogą PFO jest u dzieci zjawiskiem rzadkim. Przezskórne zamknięcie PFO jest w tej grupie chorych zabiegiem bezpiecznym i skutecznym. Kontrastowa ultrasonografia przezczaszkowa stanowi przydatną metodę w wykrywaniu i monitorowaniu skuteczności zamknięcia PFO u tych pacjentów.

Słowa kluczowe: epizod naczyniowy mózgu, zatorowość paradoksalna, przetrwały otwór owalny, przezskórne zamknięcie

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