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Silent cerebral emboli following percutaneous closure of atrial septal defect in pediatric patients: a diffusion-weighted MRI study

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PURPOSE
The aim of this prospective study was to investigate the incidence of silent cerebrovascular embolic events associated with percutaneous closure of atrial septal defect (ASD) in pediatric patients.

METHODS
A total of 23 consecutive pediatric patients (mean age, 10.4±3.8 years; range, 4–17 years) admitted for transcatheter closure of ASD were recruited in the study. The patients were scanned with a 1.5 Tesla clinical scanner. Two cranial magnetic resonance imaging (MRI) examinations were acquired before the procedure and within 24 hours following the catheterization. MRI included turbo spin-echo fluid-attenuated inversion recovery (FLAIR) sequence and diffusion-weighted imaging technique with single-shot echo-planar spin-echo sequence. The transcatheter closure of ASD was performed by three expert interventional cardiologists. Amplatzer septal occluder device was implemented for the closure of the defect. No contrast medium was administered in the course of the procedure.

RESULTS
None of the patients had diffusion restricted cerebral lesions resembling microembolic infarctions on postprocedural MRI. Preprocedural MRI of two patients revealed nonspecific hyperintense white matter lesions on FLAIR images with increased diffusion, which were considered to be older ischemic lesions associated with previously occurred paradoxical embolism.

CONCLUSION
The current study suggests that percutaneous closure of the ASD, when performed by experienced hands, may be free of cerebral microembolization in pediatric patients. However, due to the relatively small sample size, further studies with larger patient groups are needed for the validation of our preliminary results.

Acute symptomatic cerebral infarction associated with percutaneous cardiovascular intervention has been reported to have an incidence of 0.09%–1.0% when evaluated solely with neurologic examination (1–4). However, asymptomatic cerebral microemboli detected with transcranial Doppler ultrasonography (US) monitoring and diffusion-weighted imaging (DWI) following either conventional or interventional cardiac catheterization is unexpectedly more common (4–10). The incidence revealed with DWI studies varies between 3.3% and 77% depending on risk factors associated with the patient population and the procedure, in adult studies (9, 10).

Due to technologic developments, more children with congenital heart disease are taken to the cardiac catheterization laboratory for interventional treatment. The subclinical focal neurologic events are more difficult to reveal solely with neurologic examination in children compared with the adult age group. Therefore, it is crucial to determine the silent neurologic complications and the risk factors associated with heart catheterization in the pediatric population. There have been a few studies in adults (10–12), but to the best of our knowledge, no clinical studies revealed the association of subclinical ischemic lesions with transcatheter closure of atrial septal defect (ASD) in pediatric patients.

Transcatheter closure of ASD, which is an alternative to open heart surgery, is applied as a first-line treatment modality in appropriate patients (13). Despite increasing rates of complete closure with ongoing technologic innovations, neurologic complications associated with peri-interventional cerebral embolism have been reported (10, 11). In this single-center, prospective study, we aimed to investigate the incidence and the risk factors of silent cerebral embolism following transcatheter closure of ASD with the Amplatzer septal occluder (AGA Medical Corp.) device in pediatric patients.

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Methods

Patients

Between January and August 2014, 23 consecutive pediatric patients admitted for transcatheter closure of ASD were recruited in this study. There were 12 male and 11 female patients with a mean age of 10.4±3.8 years (range, 4–17 years). Exclusion criteria included presence of any systemic disease that poses a potential risk for cerebral ischemia including hematologic problems (history of deep vein or pulmonary vein thrombosis), malignancy, nephrotic syndrome, collagen tissue disease, severe pulmonary or systemic hypertension, chronic drug use including corticosteroids and oral contraceptives, bradycardia and consecutive resuscitation during the procedure, and general contraindications to magnetic resonance imaging (MRI) including severe claustrophobia or having metallic devices not compatible with MRI. In order to eliminate the need of sedation for image acquisition, patients younger than four years of age were not included. Prior to the procedure, lower extremity Doppler US examination was performed to rule out deep vein thrombosis. The presence of focal neurologic impairment was investigated with neurologic examination before and after the procedure. The study complied with the Declaration of Helsinki and was approved by the institutional review board. Written informed consent was obtained from the legal guardians of the patients.

Cardiac catheterization

The indications for ASD closure were >1.5:1 pulmonary-to-systemic flow ratio and volume overload revealed by transesophageal echocardiography (TEE). Salicylic acid 5 mg/kg/day per oral was initiated 48 hours prior to the procedure. The transcatheter closure of ASD was performed by three expert interventional cardiologists with >10 years of experience in cardiac catheterization. Unfractionated heparin 100 IU/kg was administered intravenously to all patients initially to maintain a rate of >200 s activated clotting time. The procedure was performed under general anesthesia using propofol (Diprivan, AstraZeneca Pharmaceuticals). A soft-tipped 0.035-inch guidewire was inserted following femoral vein puncture. An incompletely inflated (<1 atm) 24 mm or 36 mm balloon (NuMED Inc.) was advanced over the guidewire. The balloon was inflated until a significant indentation was detected on the balloon and shunting disappeared on TEE. The balloon was not fully inflated to avoid an inadvertent enlargement of the defect. Following the extraction of short femoral sheath, an appropriately sized (6F–9F) Mullins delivery sheath (Cook, Inc.) was advanced into the left upper pulmonary vein over the guidewire. Amplatzer septal occluder was subsequently inserted into the sheath and advanced via delivery system to the left atrial side. After opening the left atrial disc, the system was retracted and left atrial disc was positioned on the left side of the interatrial septum. A residual right-to-left shunt was ruled out and correct positioning was confirmed with the guidance of fluoroscopy and TEE; intravenous contrast medium injection was not administrated to any patients.

The total duration of the procedure and fluoroscopy time was recorded (mean duration, 44.9±15.8 min and 9.7±4.5 min; for procedure and fluoroscopy, respectively) (Table).

Main points

- Diffusion-weighted imaging (DWI) studies have reported association of percutaneous closure of ASD and procedure-related silent cerebral embolic lesions in adult patient groups.
- Current study is the first DWI study to investigate whether there is an association between percutaneous closure of ASD and silent cerebral microemboli in pediatric patients.
- We did not detect any diffusion restricted, procedure-related cerebral-cerebellar microembolic lesions on DWI.
- Percutaneous closure of ASD in pediatric patients may be free of cerebral complications in experienced hands.

Magnetic resonance imaging

All patients were examined using a 1.5 Tesla MRI system (Magnetom Aera, Siemens Healthcare) with a standard head coil. Patients underwent first cranial MRI on the day before the procedure and a control MRI was acquired within the first 24 hours and at least six hours after the heart catheterization to avoid hyperacute stage of a possible stroke event. Therefore, the mean time interval between the procedure and postprocedure MRI was 8.20±2.12 hours (range, 6.08–10.32 hours). MRI examinations included turbo spin-echo fluid-attenuated inversion recovery (FLAIR) sequence (TR/TE, 9000/84; TI, 2500 ms; FOV, 260 mm; slice thickness, 5 mm; matrix, 256×256; gap, 0.5 mm) and DWI technique performed with single-shot spin-echo echoplanar sequence (TR/TE, 6800/89, slice thickness, 5 mm, FOV, 230×230 mm; matrix, 128×99; gap, 0.5 mm) at two b values; 0 s/mm^2 and b max of 1000 s/mm^2. All image acquisitions were in the axial plane. Apparent diffusion coefficient (ADC) maps were generated by the scanner automatically, the noise threshold was set to 20. Subsequently, FLAIR, DWI, and ADC maps were transferred to a clinical workstation (Syngo MR D13, Siemens Healthcare) and two pediatric radiologists (G.K. and S.D., with three and eight years of experience, respectively) evaluated the images with consensus.

Results

The implantation was successfully achieved in all patients, and no residual shunt was observed on 24-hour control. No complication such as bleeding of the groin, pulselessness, arrhythmia, malposition of the device, residual shunt, heart valve insufficiency, or syncope was experienced within the periprocedural period or during the follow-up (mean, 13 months). Neurologic examination of the patients following the procedure revealed no abnormal focal neurologic deficit. The demographic characteristics of the patients are summarized in the Table.

In two patients out of 23, hyperintense, scattered, subcortical white matter lesions located in frontal and parietal lobes at the level of centrum semiovale were detected on FLAIR images prior to the procedure. The mean size of the lesions was 6±1.8 mm (range, 4–9 mm). Since the lesions were distributed within the internal border zone of watershed, they were considered to have occurred due to previous paradoxical embolisms. Both patients were 15 years old, female and had moderate pulmonary hypertension (Fig.). None of the patients revealed diffusion-restricted microembolic cerebral lesions. Therefore, no statistical analysis could be performed to determine the association of transcatheter closure of ASD and cerebral microembolic lesions and their risk factors.

Discussion

Patients with ASD or patent foramen ovale (PFO) have been found to be at increased

risk of paradoxical thromboembolism (14, 15). Although transcatheter closure of ASD/PFO has been applied to many patients to prevent those recurrent thromboembolic events, few studies focusing on adult patient groups revealed that transcatheter ASD/PFO closure itself is associated with periprocedural cerebral microembolic lesions. The incidence of cerebral lesions associated with ASD/PFO closure has been reported to be 0%–8.6% in adult patients (7,10–12). In the current study, as the first DWI study investigating the incidence of cerebral microembolic lesions that appear following ASD closure in pediatric patients, no association was identified between the procedure and the cerebral lesions.

Possible mechanisms of silent or symptomatic cerebrovascular paradoxical embolism associated with transcatheter closure of ASD/PFO in the early period (within the first 48 hours after the procedure) may be as follows: 1) movement of the venous thrombus from the lower extremities to the left heart during advancement of the thick long delivery sheath into the left atrium; 2) air embolism created during saline flush or contrast agent injections into the right atrium to control the residual shunt; 3) pressure alteration and air vacuum caused by the sudden rapid withdrawal of the long inner guidewire; 4) microemboli coming off the infirm and mobile rim of the interatrial septum during the sizing of the balloon (16–19). Although aforementioned risk factors may reveal the potential mechanisms of cerebral microembolic lesions associated with transcatheter closure of ASD, further studies with larger pediatric patient groups will help to reveal additional risk factors.

Previous studies have demonstrated the thrombus in or on catheter/guidewire, air embolism, scraping debris from atheroma plaques within aorta as risk factors for cerebrovascular microembolic lesions occurring following diagnostic and interventional cardiac catheterization (16, 17). In two prospective randomized studies, middle cerebral artery monitorization with transcranial Doppler US displayed that two-thirds of the microemboli occurred during the injection of saline and contrast medium. Therefore, cerebrovascular emboli were interpreted to occur often due to air embolism (18, 19). Although no contrast material was administrated, significant amount of saline was flushed during the procedure in the current study. Since the injection/flushing technique plays a crucial role in occurrence of air embolism, the cardiologists performing the catheterization took the following precautions to avoid introducing air through the sheath-catheter: 1) check the injector to make sure that it is oriented in nose-down direction, filled with saline, and free of air, 2) keep the proximal end of the catheter below the level of left atrium, 3) use Amplatzer septal occluder, as it has no side arms and avoids air embolism introduced by the side arms. The aortic arch atheroma and its contact with the catheter, duration of the procedure and the fluoroscopy have been reported as additional risk factors (9, 19, 20). In our patient group, other reasons for lack of cerebrovascular embolic events may include entry through the pulmonary veins only for

Table. Patient demographics and procedure characteristics

Age (years)	10.4±3.8 (4–17)
Gender (male/female), n (%)	12/11 (52/47)
Weight (kg)	40.0±14.4 (14–60)
ASD diameter on TEE (mm)	16.0±5.5 (9–26)
Device diameter (mm)	16.8±5.1 (9–25)
Qp/Qs	2.2±0.5 (1.5–3.2)
PVR (Wood/U/m^2)	1.67±0.38 (0.9–2.4)
Duration of the procedure (min)	44.9±15.8 (14.0–85.0)
Fluoroscopy time (min)	9.7±4.5 (3.0–18.0)
Time from procedure to second MRI (h)	8.20±2.12 (6.08–10.32)

Continuous variables are presented as mean±standard deviation.
ASD, atrial septal defect; TEE, transesophageal echocardiography; Qp/Qs, pulmonary-to-systemic flow ratio; PVR, pulmonary vascular resistance; MRI, magnetic resonance imaging; h, hour.

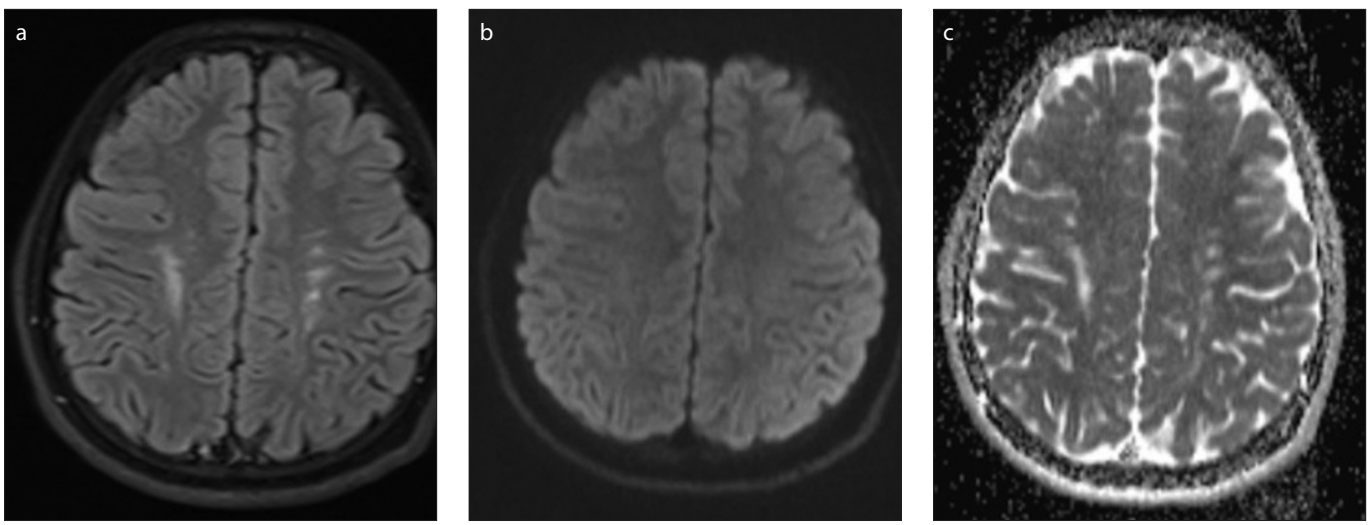

Figure. a–c. White matter lesions on bilateral frontoparietal lobes at the level of centrum semiovale in a 15-year-old girl detected on preprocedure MRI. Axial FLAIR image **(a)** reveals hyperintense white matter lesions that are confluent on the right side. Note that the lesions have no diffusion restriction **(b)** and show elevated ADC compared with normal brain parenchyma **(c)**. Based on location, these lesions were considered to have occurred as a consequence of previous paradoxical embolisms.

the left heart catheterization, and not dealing with high-risk vessels for plaque embolization such as the aorta. Furthermore, complete closure of the defect with no residual shunt following the procedure and young age may be additional factors contributing to the lack of any cerebrovascular complications (21). The total duration of catheterization and fluoroscopy are independent risk factors for the occurrence of microembolic infarctions, since the increased duration allows the catheter to interact with vessel wall during the manipulation and form thrombus (22, 23). Fairbarn et al. (9) reported the highest rate (77%) of detected cerebral ischemic lesions associated with cardiac catheterization. The procedure and fluoroscopy time were reported as 68±26 min and 22±6 min, respectively, which are longer than the ones reported in the current study (44.9±15.8 min and 9.7±4.5 min).

DWI has been reported to detect ischemic brain tissue as early as within minutes with lower false-negative rates compared with conventional MRI sequences and computed tomography, which have up to 60% false negativity particularly during the acute stage (24–26). However, during the hyperacute stage, which is defined as up to six hours following the insult, DWI may be inconsistent and not help define new ischemic lesions (27). Therefore, the time interval between procedure and second MRI examination was set to at least six hours to eliminate the possibility of false negativity for detection of microemboli. Another reason for false negativity of DWI has been suggested to depend substantially on the size and location of the lesions. The lesions with small size may not be detected due to limited spatial resolution of DWI. In those cases, incorporation of sequences with higher resolution as FLAIR helps for the detection. Fairbarn et al. (9) and Omran et al. (22) reported that DWI itself could discern microembolic lesions as small as 1 mm following transcatheter aortic valve catheterization.

This study has some limitations to be considered. The study had a relatively small number of patients with low risk factors, no systemic diseases, and no tendency to thrombosis. Further studies with larger and heterogeneous, high-risk patient populations are needed to investigate the association of cerebral microembolism, transcatheter ASD closure, and potential risk factors. Due to ethical considerations arising from the need of sedation for MRI acquisitions in very young patients, the lower age limit of the patient group had to be set to four years. Another shortcoming is that although susceptibility-weighted MRI is a more sensitive method compared with conventional sequences and DWI for the detection of both cerebral air and microbleeds associated with stroke, we did not prefer to incorporate it into our MRI protocol in order to image an unsedated pediatric patient group without prolonging the acquisition time. Finally, because no cerebral microembolic lesions were discerned, independent risk analysis could not be performed.

In conclusion, although our study suggests that percutaneous closure of the ASD with Amplatzer septal occluder in experienced hands may be free of cerebral microembolization in pediatric patients, further studies with larger patient groups are needed to validate our preliminary results.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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