Headache after transcatheter closure of atrial septal defect: An attempt to explain its origin in the pediatric population

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ABSTRACT

Background: Transcatheter closure of atrial septal defect (ASD) has become the treatment of choice for most patients. About 5% of them suffer from transient headache episodes (THE) after the procedure, whose etiology is unclear.

Aims: To evaluate risk factors for THE occurrence after transcatheter closure of ASD in the pediatric population.

Methods: Eight hundred and forty patients, after transcatheter ASD closure with nitinol devices, from a single center, were included in retrospective analysis. THE was defined as occurring up to 24 hours after the procedure. A logistic regression model including age, weight, ASD diameter, device size, presence of nitinol coating on the device, fluoroscopy time, application of balloon calibration, device oversizing, and residual shunt after 24 hours was created to evaluate risk factors for THE occurrence.

Results: There were 40 patients with THE (4.8%), 70% female and 30% male. The median age was 13 (7.35–16) years. In patients with headache, balloon calibration (BC) was performed more frequently (82.5% vs. 43.3%; P <0.001). The balloon waist median (interquartile range [IQR]), 19 (16–22) mm vs. 15 mm (12–18) mm (P <0.001), and device size median (IQR), 18 (13.5–22) mm vs. 14 (11–17) mm (P <0.001) were larger, and residual shunt after 24 hours (12.5% vs. 4.9%; P = 0.03) and a year (7.5 vs. 1.0%; P <0.001) were more frequent. ASD size and the prevalence of double/multiple ASD were similar in both groups. Age, BC application, no nickel release protection, duration of fluoroscopy, and device oversizing were predictors of THE (P <0.001).

Conclusions: BC during percutaneous ASD closure and the lack of a protective layer against nickel release on the device are risk factors for headache occurrence in the early postprocedural period.

Key words: balloon calibration, headache

INTRODUCTION

Atrial septal defect (ASD) is one of the most common congenital heart diseases (CHD) and accounts for 10%–15% of all CHD. Transcatheter closure of ASD has become the treatment of choice in most patients [1, 2]; however, defects too large for device closure or with unfavorable anatomy still need a surgical approach.

Recommended treatment age for ASD is 3–6 years old [3]. Typical symptoms such as fatigue, loss of exercise tolerance, and supraventricular arrhythmia build up slowly and are not present till adulthood [4]. Small defects (below 8mm diameter) may spontaneously close. Nevertheless, in some infants, we observe growth retardation [5], and larger ASDs may increase in size as the child grows, which forces us to perform percutaneous closure in selected younger patients [3].

Most of the devices designed for ASD closure are constructed with a nitinol (titanium and nickel alloy) self-expandable and double-disc wire mesh, filled with a polypropylene fabric, which seals the implant [6]. The general principle when selecting device size is that it should match or slightly exceed the ASD diameter [7]. Ultrasonography, especially three-di-

WHAT'S NEW?

Headaches following transcatheter closure of atrial septal defect (ASD) are a known complication. Their etiology has not been fully elucidated. In many studies, authors emphasized the role of nickel released into the serum from the implant. In our work, we have also demonstrated the impact of balloon calibration of ASD diameter on the occurrence of postoperative headaches in these patients. To our best knowledge, this is the first article to report the influence of balloon calibration on headache episodes after ASD closure. Operator experience with the calibration balloon can minimize the frequency of headaches. The procedure itself should be reserved for special cases, and the ASD dimensioning should be assessed by other techniques, especially three-dimension echocardiography.

mensional, is the preferred method to evaluate ASD size, morphology, and rims. Transesophageal echocardiography (TEE) is most widely used to navigate during ASD device closure; however, transthoracic or intracardiac ultrasonography is also feasible [8]. In selected defects, evaluation by ultrasonography alone is insufficient (particularly in small children, in whom three-dimensional imaging is impossible), which makes balloon calibration (BC) of the ASD the proper approach [9, 10]. The most severe complications of ASD device closure, namely, device embolization and erosion, may result from under- and overestimation of device size (mismatch), which is a well-known hazard [11]. Up to 5% of patients after transcatheter ASD closure suffer from transient headache episodes (THE) [12, 13]. The etiology of this phenomenon has not been clearly explained so far, however, a few hypotheses have arisen (described in the discussion section). This study aimed to evaluate risk factors for THE occurrence after transcatheter closure of ASD in the pediatric population.

METHODS

Study design

Of over 1500 consecutive patients who underwent transcatheter closure of ASD between 1997 and 2017 in a single tertiary center [14], all 851 pediatric patients (up to 18 years old) were included in the retrospective, descriptive, and nonrandomized analysis. Medical records, hemodynamic and echocardiographic data, and periprocedural and one-year follow-up results were obtained from our registry to predefine the risk factors for THE occurrence in the periprocedural period. Unsuccessful device implantation, device embolization (regardless of the method of retrieval and subsequent defect closure), major periprocedural complications (noted within 24 hours), and nickel skin allergy were the exclusion criteria. Death, stroke, tamponade, and severe arrhythmias were qualified as major complications. The indications and contraindications for ASD closure were consistent with the American Heart Association statement [15]. The study was approved by the university research ethics committee. Written informed consent was obtained from all caregivers (and children >16 years old) before the procedure.

Data analysis

Statistical analyses were performed using Statistica 13.3 software (StatSoft Inc.). All continuous variables are expressed as median with IQR (interquartile range [IQR]), and categorical data are presented as frequencies and percentages. The data distribution was tested using a Shapiro-Wilk test. The cohort was divided into two groups in terms of THE occurrence. Data were compared using Student's t-test, $\chi 2$ and Mann-Whitney tests, as appropriate. A stepwise backward_logistic regression model was created to evaluate the variables affecting the occurrence of THE with MedCalc software (MedCalc Software Ltd, Ostend, Belgium). Variables included in the model were: age, weight, ASD diameter, device size, presence of device coating to protect from nickel release, duration of fluoroscopy, application of balloon calibration, degree of device oversizing (device size to ASD diameter ratio), and the presence of residual shunt after 24 hours. The regression model was statistically significant with P <0.001, area under the curve (AUC) of 0.847; 95% confidence interval (CI), 0.821–0.871. A P-value <0.05 was considered to indicate a statistically significant result.

RESULTS

Total number of 840 patients were included in further analysis. There were 571 female (68.0%) and 269 male (32.0%) patients. The median (IQR) age was 5.5 (3–11) years and median (IQR) weight was 20 (14.5–28) kilograms. Overall, 11 patients were excluded. Four patients (0.5%) were excluded due to implantation failure: in three small children, the device was withdrawn due to improper position (large defects with insufficient rims), and in one teenager with a large defect, the 34 mm device caused significant mitral regurgitation and 2nd-degree atrioventricular block; after removal, the abnormalities resolved. Six patients were excluded due to device embolization (two patients needed urgent surgery), and one patient was excluded due to periprocedural tamponade.

A group of five patients (0.6%) after previous surgical closure of ASD were qualified for transcatheter closure due to significant residual shunt; a group of seven patients (0.8%) with right ventricular dysfunction and bidirectional shunt through the defect were qualified for transcatheter

Table 1. Baseline characteristics of patients and procedures

Variable		THE (+) (n = 40)	THE (-) (n = 800)	*P*-value
Female sex, n (%)		28 (70)	571 (71)	
Age, years, median (IQR)		13 (7.35–16)	5 (3–10)	<0.001
Weight, kg, median (IQR)		45 (22.4–54.5)	19 (14–37)	<0.001
BC, %		82.5 n = 33	43.3 n = 344	<0.001
Balloon waist, mm		19 (16–22)	15 (12–18)	<0.001
Device waist/ASD diameter, mm		6 (3–8)	3 (2–5)	<0.001
Device, mm		18 (13.5–22)	14 (11–17)	<0.001
Residual shunt, %	24 h	12.5 n = 5	4.9 n = 39	0.03
	1 y	7.5 n = 3	1.0 n = 8	<0.001
ASD diameter on TEE, mm, median (IQR)		12 (8–14.5)	10 (8–13)	0.19
Fluoroscopy time, min, median (IQR)		3 (2–5)	3.1 (2.2–5)	0.78
Nickel release protection, %		5 n = 2	33.3 n = 264	<0.001

Abbreviations: ASD, atrial septal defect; BC, balloon calibration; THE, transient headache episodes; TEE, transesophageal echocardiography

closure due to cyanosis. In one patient ASD was closed in a transplanted heart, and another patient had dextrocardia. Overall, 671 patients (79.9%) had single, and 169 patients (20.1%) had double/multiple ASD. In the case of 63 patients (7.5%), the atrial septum was qualified as aneurysmatic. In the case of 33 patients (3.9%), concomitant heart defects were confirmed, and the most common ones were: pulmonary valve stenosis (PS) in 19 patients, patent ductus arteriosus (PDA) in 4 patients, and ventricular septal defect (VSD) in 4 patients.

All procedures were performed in the standard manner described elsewhere [7], under general anesthesia and TEE guidance, via femoral approach, after heparin (100 IU/kg bolus) and antibiotic administration. After successful ASD closure, heparinization (controlled by activated partial thromboplastin time [APTT]) was continued for 48 hours and antiplatelet therapy (acetylsalicylic acid 3–5 mg/kg/daily) for 6 months was applied. Median (IQR) ASD diameter assessed on TEE was 10 (8–13) mm. BC was performed in 379 (45.1%) selected cases. Predominantly the Amplatzer sizing balloon was used, and in almost all patients the 'stop flow' technique was applied. BC was used in the case of aneurysmatic septum, double/multiple morphology, and in large defects. The median (IQR) balloon waist diameter (assessed on both TEE and fluoroscopy) was 15 (12–18) mm. Different nitinol wire mesh occluders were used depending on the procedure year, availability, and operator's preference: Amplatzer septal occluder (ASO) in 685 (81.5%) patients (including 9 patients with Amplatzer Cribriformis occluder), Hyperion in 52 (6.2%), Cocoon in 29 (3.5%), Cardi-o-Fix in 25 (3.0%), Figulla in 21 (2.5%), HeartR in 17 (2.0%), and Cera in 11 (1.3%) patients. ASO was applied before 2014, and HeartR devices did not have protection against nickel release (n = 570, 67.9%). Median (IQR) device diameter was 14 (11–17) mm. In 8 patients, pulmonary balloon valvuloplasty and in one patient PDA closure with a coil were performed simultaneously at the same catheterization, and those patients were not excluded from analysis. Median (IQR) fluoroscopy time was 3.1 (2.2–5) minutes. THE associated with the procedure were defined as headaches occurring up to 24 hours after ASD closure, of more than mild intensity, not reported in anamnesis and lasting no more than 24–48 hours. Control transthoracic echocardiography was performed routinely after 24 hours, before discharge, after 7 days, and after one, six, and twelve months. Residual shunts assessed after 24 hours and after a year were analyzed (observed in 5.2% and 1.3% of patients, respectively, and trivial/insignificant in all of them).

There was a total of 40 patients (females 68%) with THE (4.8%) in the population of 840 pediatric patients after percutaneous ASD closure. Patients with THE vs. without THE were older, median (IQR) 13 (7.35–16) years old vs. 5 (3–10) years old (P <0.001), and with higher weight median of 45 (22.4–54.5) kg vs. 19 (14–37) kg (P <0.001); there was no difference regarding sex. Size of the ASD measured on TEE was similar in patients with and without THE: median 12 (8–14.5) mm vs. 10 (8–13) mm (P = 0.19). The prevalence of double/multiple ASD was similar in both groups (29.0% in patients with THE vs. 25.1% without THE; P = 0.71). In patients with THE, BC was performed more frequently (82.5 vs. 43.3%; P < 0.001), and the balloon waist was larger: median 19 (IQR, 16–22) mm vs. 15 (IQR, 12–18) mm; P <0.001). The difference between the balloon waist and the ASD diameter measured on TEE was higher in the THE group: median (IQR) 6 (5–7) mm vs. 4 (3–6) mm (P <0.001). Also, the device diameter was larger in the THE group: median (IQR) 18 (13.5–22) mm vs. 14 (11–17) mm (P <0.001). The prevalence of residual shunt after 24 hours (12.5% vs. 4.9%; P = 0.03) and a year (7.5 vs. 1.0%; P <0.001) was higher in the group with THE. The above data were presented in Table 1. A stepwise backward logistic model showed that age, BC application, no nickel release protection, duration of fluoroscopy, and device oversizing were predictors of THE (Figure 2). The results of the logistic regression model

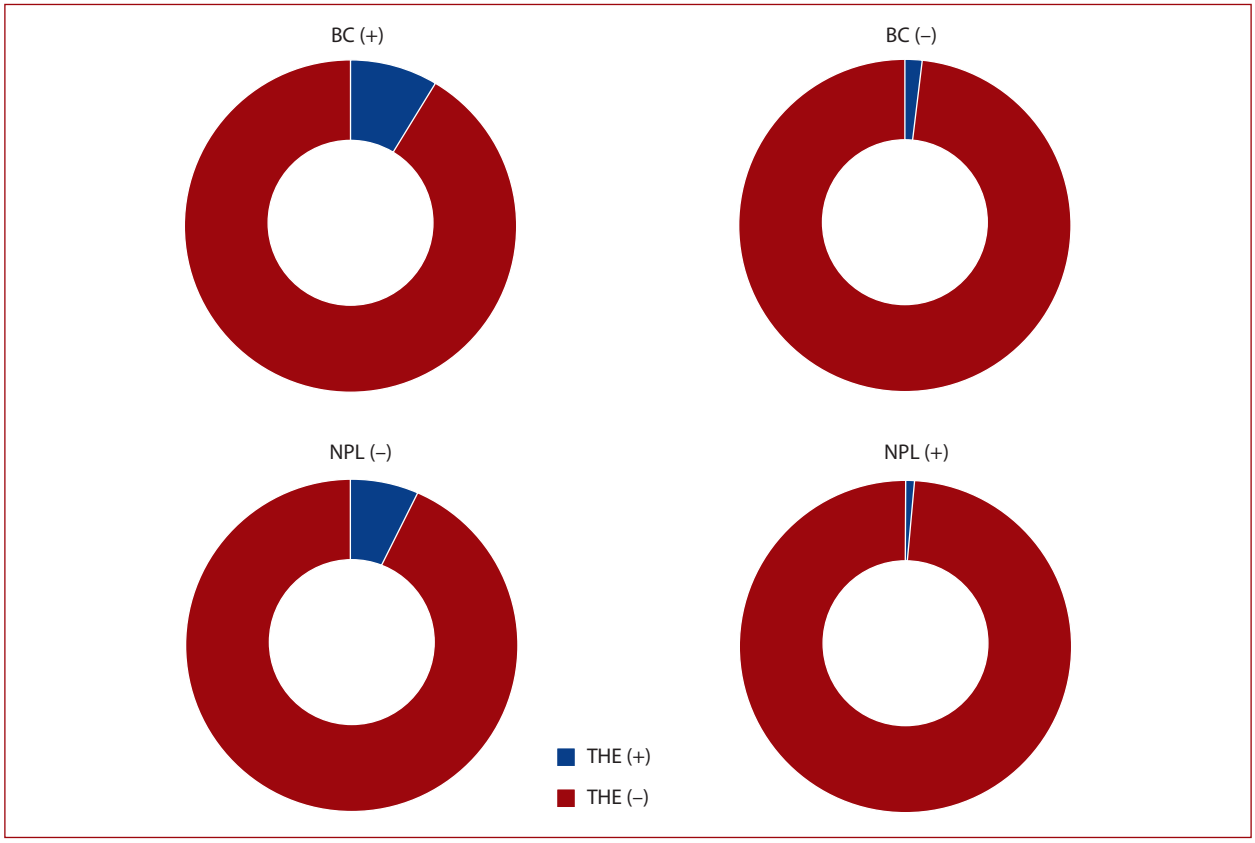

Figure 2. Influence of the use of BC and the implant without NPL on the occurrence of THE
Abbreviations: BC, balloon calibration; NPL, nickel protective layer; THE, transient headache episodes

Table 2. Predictors of THE occurrence in the regression model

Variable	Odds ratio (95% CI)
Age	1.18 (1.09–1.27)
Nickel release protection	0.13 (0.03–0.58)
Fluoroscopy time	0.91 (0.83–0.1)
Use of balloon calibration	3.68 (1.43–9.48)
Oversizing (Device size/ASD diameter ratio)	1.09 (1.01–1.19)

Abbreviations: see Table 1

are presented in Table 2. Except for short supraventricular tachycardia and transient AV II block (not requiring pharmacotherapy or pacing), no other postprocedural complications in THE patients were noted.

DISCUSSION

To our best knowledge, this is the first article to report the influence of balloon calibration on headache episodes after ASD closure. So far one of the most popular hypotheses about THE occurrence after ASD transcatheter closure is a transient increase in serum level of nickel after device deployment [3, 12, 16]. Nickel together with titanium are components of the alloy from which most devices are made. To minimize nickel release to serum, the following occluders have different protective layers: Intaglio layer in Amplatzer (after 2014), pre-oxidized nitinol in Hyperion, titanium nitride in Cera, and platinum in Cocoon. All of the Heart occluders as well as Amplatzer devices manufactured before 2014 were produced without any protective layer on the nitinol wire. Typically, the skin is the target organ for nickel, which provokes allergic eczema or dermatitis. None of our pediatric patients had an allergic history related to nickel before ASD closure. In our study, the lack of a protective layer against nickel release was found to be a factor contributing to the occurrence of THE. THE was reported in only two patients in whom a device with nickel release protection was applied (Figulla and Cardi-o-Fix). In the remaining 38 THE patients, the Amplatzer device (without Intaglio layer) was implanted. There was no THE after 2014 in the analyzed cohort. The highest nickel serum level persists only for a few weeks and then normalizes due to formation of the oxide film and calcium phosphate layer [16], which could explain the fleeting character of THE.

The limitation of our retrospective study was no possibility to measure the level of nickel and other biochemical parameters in THE patients. We were able to explain this phenomenon only by statistical analysis.

Researchers from the Clinico San Carlos associate THE with microembolism. In their opinion, headaches might result from a thrombotic substrate forming on the left-sided disk [13]. Perhaps this mechanism explains the role of BC in headache inducement as the balloon surface (even under

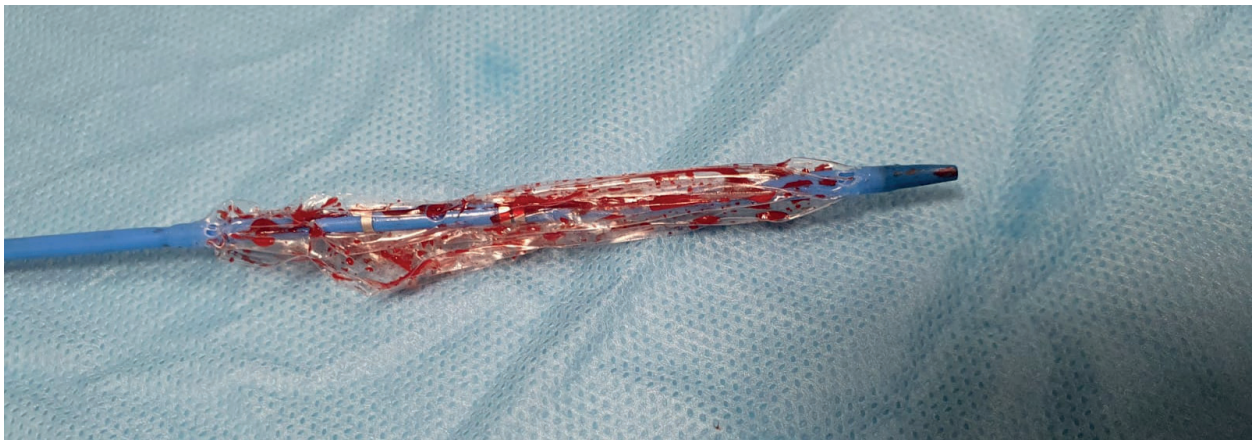

Figure 1. Numerous abundant micro-clotting on the balloon surface present despite adequate heparinization

proper heparinization confirmed with APTT) is a suitable surface for thrombi formation (Figure 1). Longer procedure time (indirectly expressed as fluoroscopy time) was also associated with risk for THE. For this reason, in our Center, we try to withdraw the balloon from the left atrium as soon as possible after defect calibration. Interestingly, regarding microembolism, logistic regression did not find a residual leak after 24 hours to be a risk factor for THE although in THE patients, residual shunt in the first 24 hours and one-year follow-up occurred more often.

Also, Wallace et al. supported the microembolic thesis using the transcranial Doppler technique. They observed many more signals during inflation of the balloon, vascular sheath placement, and device upload than in other procedure phases like hemodynamic measurements [17].

Another interesting, potential cause of THE is elevated serum level of natriuretic peptide because of atrial wall deformation after device implantation [12, 13]. Possibly, a similar wall deformation can be produced by an inflated balloon.

Carlson and co-authors noted that overestimation of the implant size increases the complication rate, but in their study, headaches were not directly mentioned [18].

It seems that BC has a significant impact on the occurrence of THE. It is worth mentioning that balloon overinflation, and thus overestimating the implant size, may result in erosion, especially in small children with low body weight [3].

On the other hand, small implants increase embolization hazard and more frequently give residual leaks after implantation [18]. Certainly, in selected cases, BC will still be helpful. In our opinion, the procedure requires balloon removal as soon as possible. Moreover, precise balloon inflation ("stop flow" technique) may minimize the problems described in this article. All observed conclusions were implemented in our institution.

The influence of BC on THE occurrence has not been investigated so far [12]. No cases of persistent neurological deficits have been reported in the literature or our follow-up lasting mean 29 months (range 6–84). Except for standard antiplatelet therapy (acetylsalicylic acid 3–5 mg/kg daily), no other treatment was necessary. Some centers recommend double antiplatelet therapy in these patients [17, 19].

There is a possibility of underestimating THE in pediatric patients, especially in the youngest children who cannot clearly describe their symptoms. Three-dimensional TEE to select the device size is an interesting alternative to BC as it is less invasive [20]. The operator's experience with the BC technique may minimize the risk of THE or even eliminate the necessity of using BC.

Article information

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