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Partial Anomalous Pulmonary Venous Return into the Inferior Vena Cava in a 28-Year-Old Female: A Variant of Scimitar Syndrome Amenable to Interventional Treatment

Scimitar Syndrome Variant

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Abstract

Scimitar syndrome is a rare congenital heart defect associated with right-sided partial anomalous pulmonary venous return (PAPVR) into the inferior vena cava (IVC). We describe the case of a 28-year-old female diagnosed with PAPVR with a typical curvilinear pattern of the right lower pulmonary vein—the so-called "scimitar sign"—on chest x-ray. Anatomical abnormalities on magnetic resonance imaging included a lower right pulmonary vein draining into the IVC and an additional vein connecting all right-sided pulmonary veins toward the left atrium. Because her anatomy was suitable, the patient underwent cardiac catheterization with occlusion of the anomalous right lower pulmonary vein with an Amplatzer Vascular Plug with excellent postinterventional results.

Key Words

PAPVR • Amplatzer vascular plug • Catheter intervention • Congenital heart disease

Introduction

The term "scimitar syndrome" was first employed by Neill et al. in 1960 to describe a rare type of partial anomalous pulmonary venous return (PAPVR) in combination with a hypoplastic right lung that receives its blood supply from systemic arteries [1]. Associated features include dextroposition of the heart, bronchopulmonary sequestration, and various extracardiac and additional cardiac anomalies. The classic radiographic finding is the "scimitar sign" on chest x-ray resulting from the curved anomalous right pulmonary vein draining into the inferior vena cava (IVC). Two forms of scimitar syndrome can be differentiated. In the infantile variant, patients usually present with tachypnea, heart failure, and pulmonary hypertension, and significant morbidity and mortality [2, 3]. In the childhood/adult form, patients are less severely affected and may be asymptomatic until a diagnosis is established. The adult variant of scimitar syndrome is commonly associated with right lung hypoplasia, abnormalities of vascular supply, dextrocardia, and abnormalities of bronchial segmentation [4]. Treatment generally implies a surgical approach, and procedural details vary depending on individual anatomic and pathologic features, as well the surgeon's preference. Procedures frequently include intra-atrial baffle repair and reimplantation of the scimitar vein into the left atrium and, if necessary, simultaneous ligation of collateral arteries supplying the right lung, right lower lobe

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resection, or even right pneumonectomy [5]. Successful attempts of interventional therapy of scimitar syndrome include transcatheter embolization of anomalous systemic arterial supply with interventional atrial septal defect closure [6] and rerouting of anomalous venous drainage to the left atrium [7].

Case Report

We present a 28-year-old female who was diagnosed with right-sided PAPVR as a variant of scimitar syndrome. The patient had been a preterm infant born at 26 weeks of gestation. She developed bronchopulmonary dysplasia and suffered from recurrent respiratory tract infections in infancy and early childhood. Her psychomotor and physical development were unremarkable. At the age of 28 years, the patient presented to our unit with exertional dyspnea. On chest x-ray, a tubular structure in the right cardiophrenic angle compatible with the typical radiologic sign of scimitar syndrome was evident (Figure 1). Subsequent MRI revealed anomalous return of the right lower pulmonary vein into the IVC. The scimitar vein was slightly stenotic proximal to its drainage into the dilated IVC. Furthermore, all right-sided pulmonary veins were connected via the scimitar vein and drained not only into the IVC but also into the left atrium, thus representing a rare variant of scimitar syndrome. The right pulmonary veins had a more tortuous appearance than usual, but no discrete stenosis was noted (Figure 2). The right ventricle was enlarged due to volume overload, and systolic function was within normal limits. The pulmonary to systemic flow (Qp:Qs) ratio, as assessed by MRI, was 1.4:1.

Cardiac catheterization was performed with the intention of interventional closure of the aberrant pulmonary vein. Levophase after right pulmonary angiography confirmed dual connection of all right pulmonary veins via the scimitar vein to the IVC, as well as to the left atrium (Figure 3A). The left-to-right shunt ratio (according to Fick) was calculated to be 1.6:1. The patient's right ventricular systolic pressure

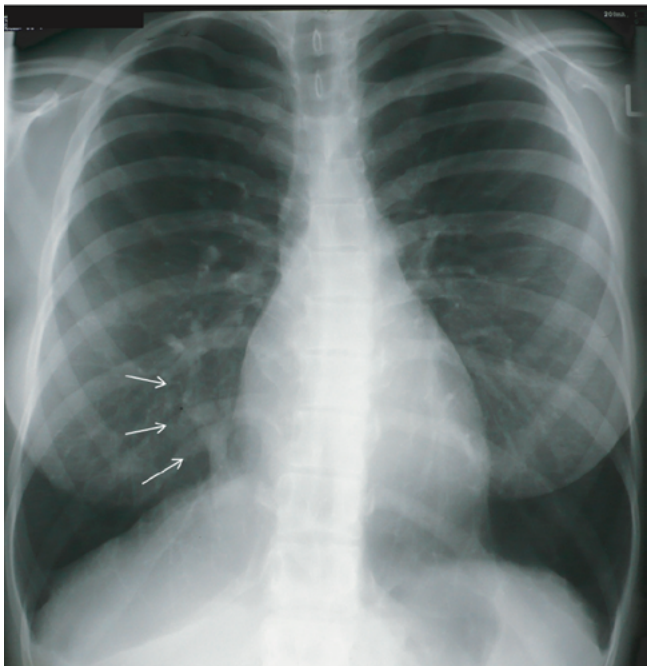

Figure 1. Chest x-ray with a classic "scimitar sign" resulting from a right pulmonary vein coursing to the right cardiophrenic angle (arrows).

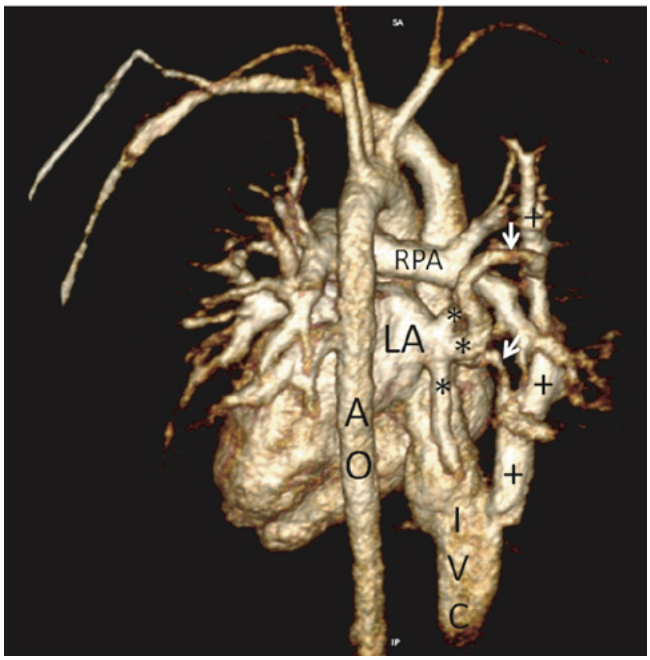

Figure 2. Three-dimensional reconstruction of cardiac MRI (posterior-anterior view). The anomalous drainage of the lower pulmonary right vein into the IVC with slight stenosis of the vessel at the diaphragm is evident. In addition, all three right pulmonary veins are connected to the left atrium. AO = descending aorta; IVC = inferior vena cava; LA = left atrium; RPA = right pulmonary artery; * pulmonary veins; + scimitar vein; arrows, additional vein connecting the lower and middle right pulmonary vein.

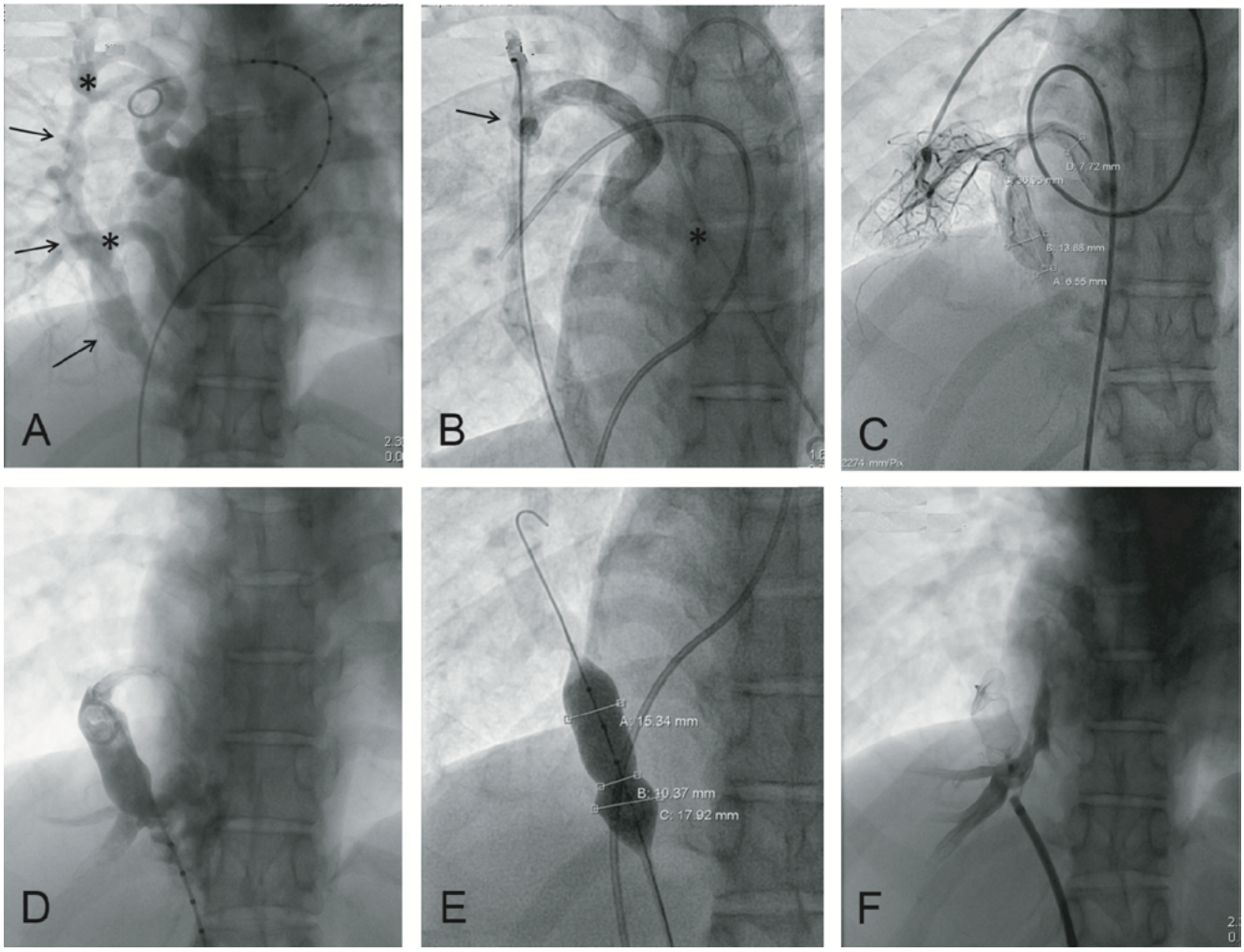

Figure 3. Cardiac catheterization (anterior-posterior views). *Panel A*. Levophase after right pulmonary angiography demonstrates typical curvilinear pattern (arrows), the so-called "scimitar sign." Drainage of the upper and middle right pulmonary veins into this descending vein (asterisks) connected to the inferior vena cava (IVC) is evident. *Panel B*. A guide catheter was directed from the IVC into the scimitar vein; hand injection of contrast demonstrates free drainage of the right upper pulmonary vein into this descending vein (arrow) and the left atrium (asterisk). *Panel C*. Diameter of the connecting vein is 13.9 mm, stenosis before drainage to the IVC 6.6 mm. *Panel D*. The lower part and stenosis of the anomalous vein are documented by direct angiography. *Panel E*. Test balloon occlusion of the lower connecting vein. *Panel F*. After implantation of an Amplatzer Vascular Plug II into the lower part of the scimitar vein, hand injection through the delivery sheath demonstrates no obstruction of the hepatic venous flow into the IVC.

was slightly elevated at 34 mmHg, and the mean pulmonary arterial pressure was 26 mmHg with an indexed pulmonary vascular resistance of 3.0 WE × m^2 and a pulmonary to systemic vascular resistance (Rp:Rs) ratio of 0.19. No pulmonary vasodilator studies were performed in the cardiac catheterization lab. The right pulmonary veins were tortuous without any obvious obstruction (Figure 3B). Angiography of the descending aorta did not reveal evidence of aortopulmonary collateral arteries. Balloon wedge angiography into the right lower pulmonary artery delineated the lower part of the scimitar vein in detail, demonstrating moderate stenosis just below the diaphragm (Figure 3C, D). Balloon occlusion of the vessel did not result in elevation of pulmonary right venous pressure or left ventricular end-diastolic

pressure, indicating that interventional occlusion was feasible. During balloon occlusion, the diameter of the connecting vein was 15.3 mm, with a stenotic segment of 10.4 × 12.7 mm (Figure 3E). Subsequently, a 20-mm Amplatzer Vascular Plug II (AVP II) was chosen to occlude this portion of the scimitar vein. The stenosis was used as the anchor for the distal waist of the device. After release from the delivery system, there was no residual shunt through the device after 10 min. Absence of obstruction of hepatic venous flow into the IVC and of the right lower pulmonary vein could be documented (Figure 3F). Repeat hemodynamic evaluation did not reveal any difference of pulmonary wedge pressure to the end-diastolic left ventricular pressure. However, the mean right pulmonary artery pressure remained elevated at 26 mmHg.

Echocardiography postimplantation showed no residual flow along the vessel occluder into the IVC. Before hospital discharge, the patient was started on a vitamin K antagonist for 6 months. No oral pulmonary vasodilator therapy was initiated after the intervention. At the 6-month follow-up, the patient was well, and the device was in an unchanged position without residual flow as assessed by echocardiography. Repeat cardiac catheterization 19 months after the intervention revealed improved hemodynamics with a slightly increased mean pulmonary artery pressure at 18 mmHg, underscoring the need for anomalous vessel closure.

Discussion

Unless patients diagnosed with scimitar syndrome are symptomatic or have a significant left-to-right shunt leading to pulmonary hypertension and right ventricular failure, clinical surveillance has been recommended, because surgery may be challenging and associated with significant complications and morbidity [8-10]. In the present case, moderate left-to-right-shunting and mild pulmonary hypertension required treatment. There was partial anomalous pulmonary venous drainage of the right lung into the IVC without further abnormalities of the right lung, including blood supply. The patient's individual anatomy with double drainage of the right lung allowed successful interventional occlusion of the inferior portion of the scimitar vein without open surgery.

Unfortunately, very few patients diagnosed with classical scimitar syndrome fulfill anatomic requirements for catheter-based rerouting of the anomalously draining vein. This case illustrates that interventional therapy should be considered and may be successful in selected patients with unusual anatomical variants.

Conclusion

Particular attention to anatomic variants of scimitar syndrome may identify novel interventional treatment options.

Conflict of Interest

The authors have no conflict of interest relevant to this publication.

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Transcatheter Closure of a Ruptured Sinus of Valsalva Aneurysm with the Amplatzer Ductal Occluder II in a 6-Year-Old Girl

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Abstract

We report the successful deployment of a 6 mm Amplatzer Ductal Occluder II via a retrograde approach to treat full occlusion of a type II ruptured right sinus of Valsalva aneurysm in a symptomatic 6-year-old girl with significant left-heart dilation.

Key Words

Occlusion • Sinus of Valsalva • Device

Introduction

Sinus of Valsalva aneurysm is a rare congenital condition accounting for less than 1% of all congenital anomalies, although the prevalence is higher in Asia. It occurs due to deficient elastic fibers in the aortic media, leading to progressive dilatation over time, and should be differentiated from acquired aneurysms caused by infections or connective tissue disorders. The right sinus of Valsalva is affected in up to 85% of cases. A classification system has been reported based on the origin of the aneurysm in relation to the right and noncoronary sinuses [1]. Rupture may be precipitated by an exertional event and usually occurs into the right atrium or ventricle, leading to significant left-to-right shunt and congestive cardiac failure. Once the clinical diagnosis has been confirmed on echocardiography, advanced imaging modalities may be used to clarify the aneurysm morphology because there may be multiple ostia from the aneurysm into the right heart, and this may influence the closure approach.

Case Presentation

A 6-year-old girl was referred with increasing fatigue and was noted to have a harsh grade IV long systolic murmur. She had bounding pulses, and chest x-ray revealed a large heart with increased pulmonary vascular markings. Transthoracic echocardiogram (TTE) demonstrated a dilated left heart with preserved systolic ventricular function and turbulent flow on color Doppler from the aortic root into the pulmonary outflow. This was initially thought to be an aortopulmonary window, but further assessment confirmed that the flow from the aortic root was entering the right ventricular outflow tract (RVOT) beneath the pulmonary valve. The jet measuring 6 mm in diameter originated from the midpoint of the right coronary sinus into the RVOT, with persistence of flow into diastole (although a diastolic component to the murmur was not clearly audible), consistent with a type II ruptured sinus of Valsalva aneurysm according to the original Sakakibara classification [1]. There was an eccentric jet of aortic incompetence graded as mild.

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Catheterization was performed in a single-plane catheterization suite with a C-arm under general anesthesia with transesophageal echocardiography (TEE) guidance. TEE confirmed the presence of a 6 mm ruptured right sinus of Valsalva aneurysm with continuous flow into the RVOT (Figure 1:Panel A and B). These findings were confirmed with ascending aortic angiography (Figure 2:Panel A). The mean pulmonary artery pressure was 26 mmHg, with right ventricular systolic pressure of 42 mmHg and ascending aortic pressures of 91/38. The ratio of total pulmonary to total systemic blood flow (Qp:Qs) measured 4.2:1 but was calculated on 100% oxygen as calculation in room air was not feasible. The defect was easily crossed with a 5-French (Fr) Judkins Right catheter and an exchange-length Glide wire with advancement of the JR4 into the distal right lower pulmonary artery. A 0.035" Amplatzer Extra-Stiff wire (St. Jude Medical, St Paul, MN, USA) was positioned in the right pulmonary artery, and the JR4 was exchanged for a 5Fr guiding sheath (Figure 2:Panel B). A 6:6 Amplatzer Ductal Occluder (ADO) II (St. Jude Medical) was then advanced across the defect, the distal disk was partially deployed, and the sheath was retraced slowly from the main pulmonary artery. As the device crossed the pulmonary valve, the distal disk of the device engaged the right ventricular aspect of the defect, and the waist was deployed within the neck of the aneurysm and finally the proximal disk in the aortic root. TEE confirmed good device positioning (Figure 1:Panel C), but it was unclear if there was a small persistent leak. There was no impingement on the aortic or pulmonary valves. It was decided to release the device because there was some tension from the delivery cable distorting the aortic end of the device away from the root. Following release, the device position was more satisfactory, and the final aortic root angiogram confirmed good position with no residual leak (Figure 2:Panel C).

The patient recovered well from the procedure with no procedural complications. Predischarge echocardiogram the following day demonstrated a good device position, but it initially appeared that there may be a small residual leak. Further assessment revealed that there was a small perimembranous ventricular septal defect (VSD) just beneath the right coronary cusp of the aortic valve that was not initially noticed due to its proximity to the more prominent jet from the ruptured sinus of Valsalva aneurysm. The flow pattern was systolic with no diastolic component and a peak estimated systolic gradient of 82 mmHg. There was no RVOT obstruction or increase in the degree of mild aortic incompetence.

Discussion

Although surgical repair of ruptured sinus of Valsalva aneurysm has been extensively described [2], reports of transcatheter closure are sparse [3-9]. The largest study to date reported 18 successful cases from 20 attempts with a median age of 23 years (17–52 years) [3]. The majority of patients were symptomatic, and few had associated lesions such as VSDs, which were reported in 41% of 725 patients from a large systematic review [2]. In all patients, the defects were closed from the venous side using ADOs 2–4 mm larger than the aortic end of the defect. The ADO sizes ranged from 8/6 to 16/14 mm. Thirteen

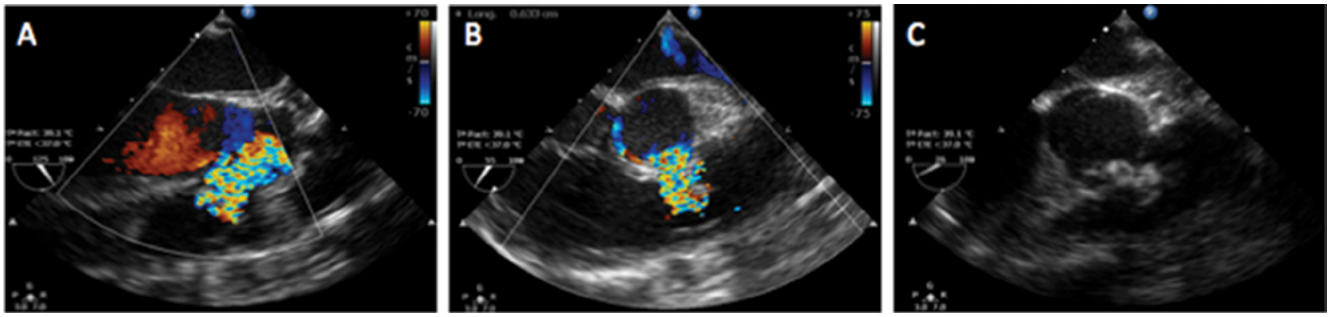

Figure 1. Series of transthoracic echocardiogram images demonstrating the color flow across the ruptured sinus of Valsalva aneurysm from the right coronary sinus into the right ventricular outflow tract in the long (*Panel A*) and short (*Panel B*) axes. (*Panel C*). The Amplatzer Ductal Occluder II is in a good position across the ruptured aneurysm following release.

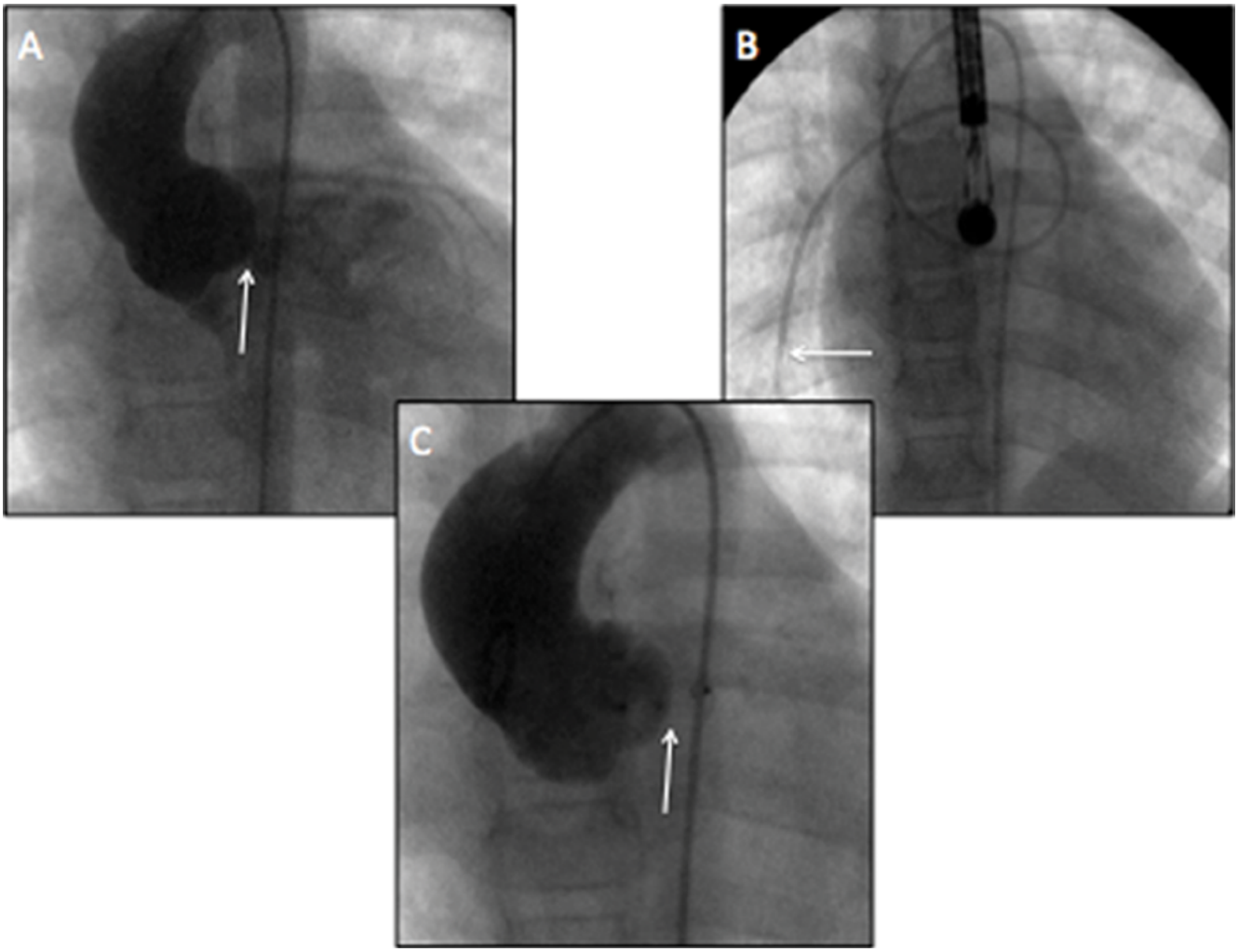

Figure 2. *Panel A.* Initial ascending aortogram demonstrates the sinus of Valsalva aneurysm (white arrow) with rupture into the right ventricular outflow. Mild aortic regurgitation is evident. *Panel B.* Outline of the guiding sheath across the defect from the aorta and positioned distal in the right pulmonary artery. *Panel C.* Final ascending aortogram demonstrates the Amplatzer Ductal Occluder II in a good position (white arrow) with ne residual flow across the ruptured aneurysm.

patients had complete closures at discharge. Five had a residual shunt (four small and one moderate with self-abating hemolysis). Trivial aortic regurgitation (AR) occurred in four. On median follow-up of 24 months (range 1–60 months), 15 patients were in New York Heart Association class I. The residual shunt disappeared in three and was small in two; procedure-related AR vanished in two of four. There was no AR progression, recurrence, infective endocarditis, or device embolization. A variety of other devices have been described in case reports with good success [4-9]. The majority of these closures were in adult patients with delivery from the femoral venous approach following the creation of an arteriovenous loop. In our case, the patient was young, and the low profile of the ADO II allowed us to retrogradely deliver the device from the aorta without the need to create an arteriovenous loop or use a stiff sheath and dilator, which may be more likely to induce hemodynamic instability in a small child. The waist of the device was delivered within the aneurysmal sac toward the aortic end to ensure optimal flow occlusion from the higher pressure aorta. There was no impingement on the aortic or pulmonary valves, and the "soft" nature of the device, which has made it popular for closing perimembranous VSDs [10], was attractive to ensure

minimal distortion of the aortic root in a smaller child. The occlusive nature of the device has been well reported in high flow defects such as VSDs and patent ductus arteriosus [10, 11].

The learning point from the case was to ensure full interrogation of the ventricular septum prior to closure. A small perimembranous VSD may be easily overlooked, especially considering the turbulence seen on color imaging from the right sinus of Valsalva throughout the cardiac cycle. The perimembranous region of the septum is separated from the aortic root only by the thin leaflets of the aortic valve. In retrospect, knowledge of this defect would not have changed our approach. It is arguable that the VSD may have been contributing to the mild AR; however, AR has been reported in up to 71% of patients with ruptured sinus of Valsalva aneurysms [2], which is far greater than seen with a small perimembranous VSD. It is arguable that the device may provide some support to the right sinus and consequently to the support structure of the right coronary cusp to mitigate against further AR.

We elected to use low-dose aspirin following device implantation to limit the risk of thromboembolism. The evidence for such an approach is not strong; however, it has been a widely prescribed practice with device closure where the left-sided discs are proximal to the cerebral circulation origin.

Conclusions

In conclusion, ruptured sinus of Valsalva aneurysms are exceedingly rare in children, but transcatheter closure is feasible, and the ADO II may be an attractive device choice to minimize aortic root distortion.

Conflict of Interest

The authors have no conflict of interest relevant to this publication.

Comment on this Article or Ask a Question

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A Practical Scoring System to Select Optimally Sized Devices for Percutaneous Patent Foramen Ovale Closure

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Abstract

Background: **Patent foramen ovale (PFO) has been linked to cryptogenic stroke, and closure has been reported to improve clinical outcomes. However, there are no clear guidelines to direct device sizing. This study sought to use patient characteristics and echocardiographic findings to create a prediction score for device sizing.**

Methods: **This was a retrospective review of patients undergoing percutaneous PFO closure at our institution between July 2010 and December 2014. Demographic and clinical characteristics were recorded, and all pre- and intraprocedural echocardiography results were evaluated.**

Results: **Thirty-six patients underwent percutaneous PFO closure during the study period. All procedures were performed using an Amplatzer Septal Occluder "Cribriform" (ASOC) device in one of three disc diameters: 25, 30, or 35 mm. Closure was indicated for cryptogenic stroke/transient ischemic attack in 75% of cases. Every case (100%) was successful with durable shunt correction at the 6-month follow-up without complications of erosion or device embolization. The presence of atrial septal aneurysm (ASA) (p = 0.027) and PFO tunnel length >10 mm (p = 0.038) were independently associated with increased device size. A scoring system of 1 point for male sex, 1 point for ASA, and 1 point for PFO tunnel >10 mm long was associated with the size of closure device implanted (p = 0.006).**

Conclusions: **A simple scoring system may be used to select an optimally sized device for percutaneous PFO closure using the ASOC device.**

Key Words
Patent foramen ovale • Device sizing • Percutaneous closure

Introduction

A patent foramen ovale (PFO) is a remnant of fetal circulation. In utero, placental blood from the inferior vena cava is directed toward the interatrial septum and across the foramen ovale, facilitating flow of oxygenated blood into systemic circulation. At birth, decreased pulmonary artery and right heart pressures result in a reversal of the right atrium-to-left atrium pressure gradient across the foramen ovale. This change in pressure pushes the septum primum (left atrial flap) against the septum secundum (muscular atrial septum). These structures typically fuse together in the first two years of life. Incomplete fusion results in a slit-like defect that is present in approximately 25% of adults and is referred to as a PFO [1, 2]. The presence of PFO has been associated with an increased risk for paradoxical embolism resulting in stroke or obstructing peripheral embolism [3-7]. PFO has also been linked to increased risk for migraine headaches, hypoxemia, decompression syndrome in divers, and the platypnea-orthodeoxia syndrome [8-10]. The severity of these associated illnesses, particularly the potentially devastating complications of cryptogenic stroke, has increased interest in PFO closure.

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Transcatheter PFO closure may be performed with a variety of closure devices, which are manufactured in multiple sizes. Appropriate sizing of the selected device is critical to ensure adequate closure of the defect, minimize the likelihood of embolization, and avoid erosion of nearby cardiac structures. Too-large devices have been associated with erosion and an increased risk of atrial fibrillation [11, 12]. Conversely, devices that are too small increase the risk of incomplete closure and are at risk for embolization [13].

While there are clear guidelines for the sizing of atrial septal defect (ASD) closure devices, including use of the stop-flow technique, at this time, there is no consensus regarding the selection of closure device size for PFO closure when utilizing the Amplatzer Septal Occluder "Cribriform" (ASOC) device (St. Jude Medical, SJM; St. Paul, MN, USA) for off-label closure of symptomatic PFOs. The instructions for the use of the ASOC, which is intended for ASD closure, suggest device size selection that maximizes device size such that the radius of the discs does not exceed the shortest distance from the defect in the septum to either the aortic root or superior vena cava (SVC) [14]. These criteria ensure that the device is large enough to cover fenestrated ASDs without impinging surrounding structures. Sizing balloons may be used to approximate the diameter of a PFO [15]. However, the compliant nature of the septum primum and secundum make this technique imprecise, and the use of a sizing balloon carries the risk of interatrial septum rupture [16]. Currently, PFO device size is selected at the discretion of experienced operators, who may rely on anatomic factors (e.g., presence of interatrial septal aneurysm, tunnel length, shunt visualization) and clinical factors (e.g., patient age, sex, and body mass index (BMI)).

This study sought to identify patient characteristics and echocardiographic findings associated with size selection of the ASOC for PFO closure.

Methods

A retrospective review was performed of patients undergoing percutaneous PFO closure with the ASOC device at our institution between July 2010 and December 2014. Demographic and clinical characteristics were obtained. All available pre- and intraprocedural echocardiography, including transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), and intracardiac echocardiography (ICE) were evaluated. Preprocedure TTE studies were reviewed for the presence of atrial septal aneurysm (ASA), which was universally defined as atrial septal excursion >15 mm. Pre- and intra-procedural TEE and ICE were reviewed for the presence of ASA and abnormal thickening of the atrial septum (defined as >4 mm, which is the waist length of the ASOC device used in this study). In addition, measurements of pertinent atrial anatomy were also completed, including the presence and length of any appreciable PFO tract and fossa ovalis diameter. All cases were performed using the ASOC self-expanding, double-disc device. The device has a double-disc design and comprises Nitinol mesh and polyester fabric. It is manufactured in four disc diameter sizes: 18, 25, 30, and 35 mm. The 40-mm device is not currently available in the United States. Device size selection was at the discretion of the attending interventional cardiologist.

Univariate analyses of each measured variable were performed to assess for association with device size selection. Fisher's exact test was used to examine the association between the individual categorical variables and the size of the final closure device implanted. One-way analysis of variance was used for univariate analysis of continuous variables. Categorical variables that were individually associated with device size were combined with pertinent clinical variables to create a total of seven hypothesized prediction scores. These scores were tested with Kruskal-Wallis H Test and Fisher's exact test to assess the association between the proposed scoring system's score and the size of final closure device implanted. In addition, receiver operating characteristic (ROC) curves were generated to assess the sensitivity and specificity of the scores. $p < 0.05$ was considered significant. All statistical analysis was performed using STATA (StataCorp, College Station, TX, USA).

Results

A total of 36 patients underwent percutaneous PFO closure during the study period. Patient demographics, pre- and intraprocedural imaging, and PFO characteristics are listed in Table 1. The indication for closure was cryptogenic stroke/transient ischemic attack in 75% of cases. Refractory hypoxemia and overwhelming deep vein thrombosis burden accounted for the remaining 25% of cases. Each case (100%) was successful, with complete resolution of shunt at the 6-month follow-up. No cases were complicated by erosion or device embolization. In three cases, a smaller device was initially delivered across the PFO before it was determined to be too small and then removed prior to the delivery and deployment of a larger device. Two of these cases resulted in changes from 25- to 30-mm diameter devices. One case

Table 1: Summary characteristics of patients studied

No. of Patients	36
Patient Characteristics	Mean (STD)
Age	56.7 (13.8)
Male	13 (36%)
Height (cm)	168.7 (11.1)
Weight (kg)	86.3 (25.5)
BSA	1.9 (.28)
Size of Device Implanted	
25 mm Cribriform	18 (50%)
30 mm Cribriform	16 (44%)
35 mm Cribriform	2 (6%)
Indication for Procedure	
Cryptogenic Stroke/TIA	27 (75%)
High DVT Burden	3 (8%)
Refractory Hypoxia	6 (17%)
TTE, Pre-Procedure, no.	26 (72%)
TEE, Pre-procedure, no.	19 (53%)
ICE, Intra-procedure, no.	12 (33%)

BSA = Body Surface Area, calculated by DuBois criteria.
TIA = transient ischemic attack.
DVT = deep venous thrombosis.
TTE = trans-thoracic echocardiography.
TEE = transesophogeal echocardiography.
ICE = intra-cardiac echocardiography.

was a change from a 30- to a 35-mm diameter device. These cases were categorized by the final device size implanted. All procedures were performed using the ASOC device in one of three disc diameters: 25 mm (18 patients, 50%), 30 mm (16 patients, 44%), or 35 mm (2 patients, 6%).

The results of univariate analysis are listed in Table 2. The presence of ASA ($p = 0.027$, Fisher's exact test) and PFO tunnel length >10 mm ($p = 0.038$, Fisher's exact test) were independently associated with increased device size.

To guide sizing, a list of hypothesized sizing scores and their included variables is available in Table 3. A scoring system of 1 point for male sex, 1 point for ASA, and 1 point for PFO tunnel >10 mm in length was significantly associated with the size of closure device implanted ($p = 0.007$ and $p = 0.006$, Kruskal-Wallis H Test, STATA; Figure 1). ROC curves were created for each prediction score to assess sensitivity and specificity. Because of the limited number of 35-mm devices implanted in the study period ($n = 2$), 30- and 35-mm devices were grouped together for the ROC analysis. The area under the curve for the proposed sizing score was 0.8846 (STATA, Figure 2). The cutpoint score of ≥2 had 75% sensitivity and 92% specificity for a device diameter ≥30 mm.

Discussion

Percutaneous PFO closure has been proposed as a safe alternative or adjunct therapy to antiplatelet medication and anticoagulation in patients with cryptogenic stroke or peripheral embolism [10, 17-19]. Observational studies have suggested a substantial benefit to PFO closure in the secondary prevention of neurologic and vascular events when compared to medical therapy [20, 21]. Three randomized controlled trials assessing PFO closure for secondary prevention of cryptogenic stroke failed to reach their primary efficacy endpoints [22-24]. However, per-protocol and as-treated analysis of one of the randomized trials did show a significant benefit of closure over medical therapy in the prevention of recurrent ischemic stroke and death [22]. At this point, percutaneous closure of PFOs in the U.S. is considered "off-label," and there is a wide heterogeneity in device size selection.

Our study suggests that patients undergoing percutaneous PFO closure who display certain echocardiographic findings will likely require closure devices with larger disc diameters. The presence of ASA and increasing length of PFO tunnel on TEE or ICE were independently associated with larger device size. In addition, our findings suggest that a sizing score may be used to facilitate identification of patients that are likely to require larger devices. A scoring system consisting of 1 point for the presence of ASA, 1 point for PFO tunnel length >10 mm, and 1 point for male sex was statistically associated with increasing device size. Scores of 0 and 1 were associated with the 25 mm device. A score of 2 was associated with the 30 mm device, and a score of 3 was associated with the 35 mm device.

Table 2: Univariate Analysis of Patient Characteristics and Echocardiographic Findings

	25 mm Device	30 mm Device	35 mm Device	
Variable				
No. of patients	18	16	2	
No. Male	7 (39%)	5 (31%)	1 (50%)	$p = 0.87$
Age	57 (12.5)	55 (16.2)	61.5 (4.9)	$p = 0.82$
Height (cm)	170 (12)	166 (9)	176 (16)	$p = 0.43$
Weight (kg)	89.7 (31)	83.7 (19)	76 (8)	$p = 0.68$
BSA	2.0 (0.3)	1.9 (0.2)	1.95 (0.2)	$p = 0.75$
Tunnel Length (mm)	8.7 (3.2)	14.2 (6.5)	22	$p = 0.007$
Percent with:				
ASA	3 (17%)	9 (56%)	1 (50%)	$p = 0.027$
Long Tunnel	4 (31%)	6 (86%)	1 (100%)	$p = 0.038$
Thickened Septum	7 (39%)	5 (31%)	1 (50%)	$p = 0.871$

BSA = Body Surface Area. ASA = Atrial Septal Aneurysm, defined as atrial septal excursion of >15 mm.
Long Tunnel = PFO Tunnel Length on TEE or ICE >10 mm in length.
( ) denote stand deviation, unless otherwise noted.

Table 3: List of hypothesized sizing scores tested

Score		Variables Included in Score
A	$p = 0.26$	1 point each for male sex and presence of ASA
B	$p = 0.08$	1 point each for male sex, presence of ASA, and thickened septum
C	$p = 0.41$	1 point each for male sex, tall height, and presence of ASA
D	$p = 0.29$	1 point each for presence of ASA and thickened septum
E	$p = 0.21$	1 point each for thickened septum, tall height, and presence of ASA
F	$p = 0.03$	1 point each for male sex, presence of ASA, thickened septum, and long tunnel
G	$p = 0.007$	1 point each for male sex, presence of ASA, and long tunnel

ASA = Atrial Septal Aneurysm, defined as atrial septal excursion of >15 mm.
Long Tunnel = PFO Tunnel Length on TEE or ICE >10 mm in length.
P values listed are results of Fisher's Exact Test using STATA.

At this time there is no consensus regarding the selection of device size for PFO closure. A method utilizing a sizing balloon to estimate appropriate device size has been described previously [15]. However, the use of sizing balloons carries some risk and may not provide meaningful information due to the relative compliance of the tissues of the intra-atrial septum [16]. A sizing balloon sitting across a slit-like or oval-shaped PFO may not adequately measure defect length; therefore, operators typically select the size of closure device based on personal experience. This practice was reflected in the clinical trials assessing percutaneous PFO closure. In the RESPECT trial, the choice of device size was made at the discretion of the operator with the guidance of the Amplatzer PFO Occluder instructions for use [22]. This device has a larger right atrial (RA) disc than left atrial (LA) disc with a central pin. Specifically, the instructions suggest measur-

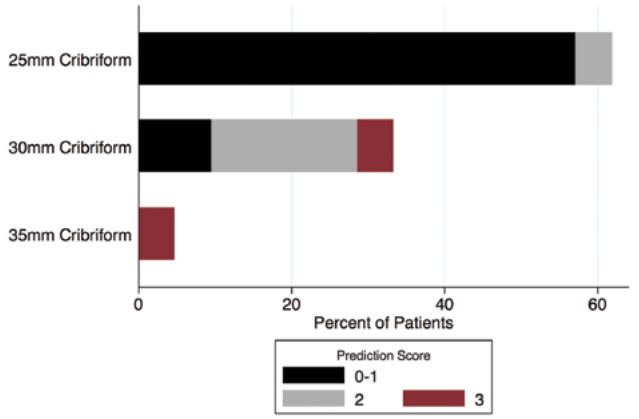

Figure 1. Percent of patients in study receiving each device size and their sizing score.The score includes 1 point for male sex, 1 point for an atrial septal aneurysm (septal excursion >15 mm on echocardiography), and 1 point for a patent foramen ovale tunnel >10 mm in length.

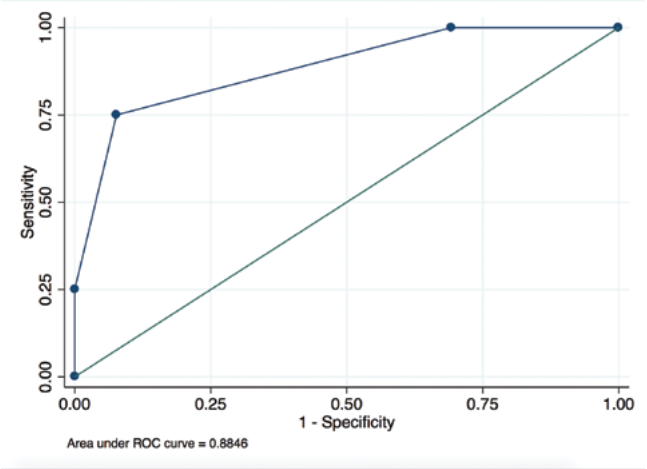

Figure 2. Receiver operating characteristic curve of the sizing score for association with implantation of an Amplatzer Septal Occluder "Cribriform" device ≥30 mm diameter. The score includes 1 point for male sex, 1 point for an atrial septal aneurysm (septal excursion >15 mm on echocardiography), and 1 point for a patent foramen ovale tunnel >10 mm in length.

ing the shortest distance from the PFO to the aortic root and SVC. The recommendations call for implantation of the 35 mm device if this distance is >17.5 mm, the 25 mm device if the distance is 12.5–17.4 mm, and a 1–8 mm device if the distance is 9–12.4 mm. If the shortest distance from the PFO to the aortic root or SVC is <9 mm, the instructions prohibit implanting the Amplatzer PFO Occluder device. The instructions do allow for the use of a larger device in the setting of ASA, but there are not specific recommendations for device size selection when ASA is present. These recommendations rely on obtaining echocardiographic measurements from the PFO to both the aortic root and SVC. These measurements may be difficult to reproduce, especially in mobile, aneurysmal atrial septa. In addition, the instructions do not account for BMI or tunnel length, which could contribute to device sliding if smaller devices are chosen. It should be noted that the Amplatzer PFO Occluder has a larger RA disc than LA disc, for example, the 35 mm device has a 25 mm left atrial disc. The difference in disc size may also contribute to device sizing, especially compared to the ASOC device that has discs of equal sizes. The CLOSURE 1 trial protocol called for sizing balloon estimation of PFO size prior to closure but did not delineate how this would inform device size selection [24]. Balloon-sizing was optional in the PC trial, and device size selection was at the discretion of the treating physician [23].

This study identified two echocardiographic findings that were independently associated with larger device requirements for PFO closure: the presence of ASA and a long PFO tunnel. Aneurysm of the interatrial septum is characterized by mobile atrial tissue that has a large distance of excursion during the cardiac cycle. This floppy tissue provides very little support for a closure device deployed across a PFO. Therefore, a larger device may be beneficial in such cases to provide additional support of septal architecture and continuously occlude the PFO. Long-tunnel PFO tracts are challenging for device closure because they require devices with either variable waist-length or large, strong discs to effectively shorten the tunnel length. All of the closures completed in our study were performed with the ASOC device, which is a strong double-disc device. Larger disc diameters of the ASOC device could provide additional strength to effectively shorten the long PFO tunnel length, which may explain why larger disc devices were used in the patients with longer tunnels. Interestingly, both ASA and long-tunnel length have been associated with risk for embolization, which may indicate that patients with these findings would benefit from larger

devices to avoid embolization [13]. There was no correlation between the presence of a right atrial Chiari network and device size selection.

Objective selection of device size with the proposed scoring system could potentially improve both the safety and cost of percutaneous PFO closure. For example, three patients in our cohort required extended procedure times to remove a device that was too small before implanting an appropriately sized device. Two of these patients had ASA on preprocedure TTE, and were, therefore, more likely to require a larger device size. Prediction of device size requirements with the sizing score could have limited fluoroscopy time and prevented the waste of a device that was too small.

Limitations

This was single-center, retrospective review of 36 patients who underwent percutaneous PFO closure with the ASOC device. No other devices were studied. Alternative devices may need additional assessment for sizing. Only 21 patients had either TEE or ICE images available for retrospective review, further limiting the functional sample size of the study. Only two patients received the largest device (35 mm), which limits any conclusions regarding association with this device size. The choice of closure device size was made at the discretion of the interventional cardiologist; therefore, our findings may be confounded by any subjective bias the operator applied in selecting a closure device. In addition, the retrospective nature of this study did not allow us to adequately assess whether the device size truly represents the optimal-sized device for each patient. Larger, prospective studies are needed to clarify this point.

Conclusions

The presence of ASA and a PFO tunnel length >10 mm were independently associated with the selection of a larger PFO closure device in this cohort of patients. A scoring system consisting of 1 point for the presence of ASA, 1 point for PFO tunnel length >10 mm, and 1 point for male sex was statistically associated with the size of device implanted. Using the scoring thresholds defined above, this score could be implemented to predict the appropriate device size required in a specific patient. Use of this prediction score could both improve patient safety and limit costs. Further prospective studies are warranted to determine the accuracy of this sizing score and whether this its use limits residual shunt and other adverse events related to percutaneous PFO closure.

Conflict of Interest

Dr. Shah is a consultant/proctor for St. Jude Medical. None of the other authors have conflicts of interest to report.

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Successful Revascularization of a Completely Occluded Right Coronary Artery by Local Thrombus Fragmentation, Thrombolysis, Thrombus Aspiration, and Balloon Angioplasty in a Patient with Atypical Kawasaki Disease

A Case Report and Review of the Literature

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Abstract

Background: **The clinical presentation of atypical Kawasaki disease (KD) is variable; thus, an accurate diagnosis may be missed. With intravenous immunoglobulin therapy, the risk of coronary arterial lesions has been reduced from 20–25% to about 5%. Coronary artery aneurysms may remain clinically silent, but thrombosis may result in acute myocardial infarction. We report a case with complete occlusion of the right coronary artery (RCA) due to thrombosis of large aneurysms and severe stenoses after atypical KD.**

Methods: **A 10-year-old boy was admitted to our tertiary medical center after two episodes of ventricular fibrillation caused by acute myocardial infarction.**

Results: Coronary angiography showed aneurysms of the left coronary artery and a completely occluded RCA. Transcatheter revascularization was achieved by a combination of mechanical thrombus fragmentation, intracoronary thrombolysis, thrombus aspiration, and balloon angioplasty of two stenosed areas of the RCA, resulting in complete reperfusion. The child´s past medical history revealed the diagnosis of untreated atypical KD 6 months previously.

Conclusions: **There are few reports of coronary interventions after KD in young patients. Coronary artery abnormalities include persistent aneurysms with the risk of thrombosis and progressive stenosis. However, no confirmed treatment guidelines exist for this particular patient group. Based on the highly variable anatomy of the coronary arteries, an individualized therapy using the full armamentarium of endovascular treatments may be necessary. This case study suggests that primary percutaneous coronary intervention using a targeted approach might be safe and effective in the treatment of acute myocardial infarction after KD.**

Key Words

Atypical • Kawasaki disease • Coronary occlusion • Intracoronary lysis • Pediatrics interventions

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Introduction

Kawasaki disease (KD) is an acute febrile disease of unknown origin, characterized by systemic vascular inflammation involving small and medium arteries, with predilection for coronary arteries. Since the first report in 1967 from Japan [1], KD has become the most common form of pediatric systemic vasculitis. The clinical presentation of KD is variable but classically consists of 5 days of fever, accompanied by nonpurulent conjunctivitis, rash on the trunk, erythema of the lips or oral cavity, erythema of hands or feet, and cervical lymphadenopathy. An atypical presentation is difficult to recognize; it may lead to delayed treatment and is thus associated with a higher incidence of coronary aneurysms (CAAs). Immediate treatment with immunoglobulins reduces the incidence of coronary artery aneurysms in children from 25% to only 5% [1].

Nowadays, CAAs following KD are the leading cause of acquired heart disease in children and young adults in western countries. Coronary artery abnormalities include persistent aneurysms with the risk of thrombosis and progressive stenosis, with or without the development of extensive collateral circulation. CAAs can persist, progress to stenosis, and lead to acute myocardial infarction [2]. There are few reports of coronary interventions after KD performed in young patients [3]; additionally, due to the highly variable anatomy of the lesions of the coronary arteries after KD, no confirmed standardized treatment guidelines for this particular patient group exist.

Here we report a case of successful and complete revascularization of thrombosed giant aneurysms of the right coronary artery (RCA) including dilatation of severe stenosis in a patient after atypical KD.

Case Presentation

A 10-year-old male child was transferred to our hospital with the presumed diagnosis of acute myocardial infarction. He suffered from two episodes of ventricular fibrillation that were successfully treated by resuscitation and defibrillation. The electrocardiogram (ECG) showed ST-segment elevation in V1 to V4 and was consistent with myocardial ischemia. The laboratory studies showed an elevated troponin I (11,232 pg/ml, Ref. 0–26; Figure 1). All other laboratory parameters were normal, including inflammatory markers. Transthoracic echocardiography showed dilatation of the central coronary arteries

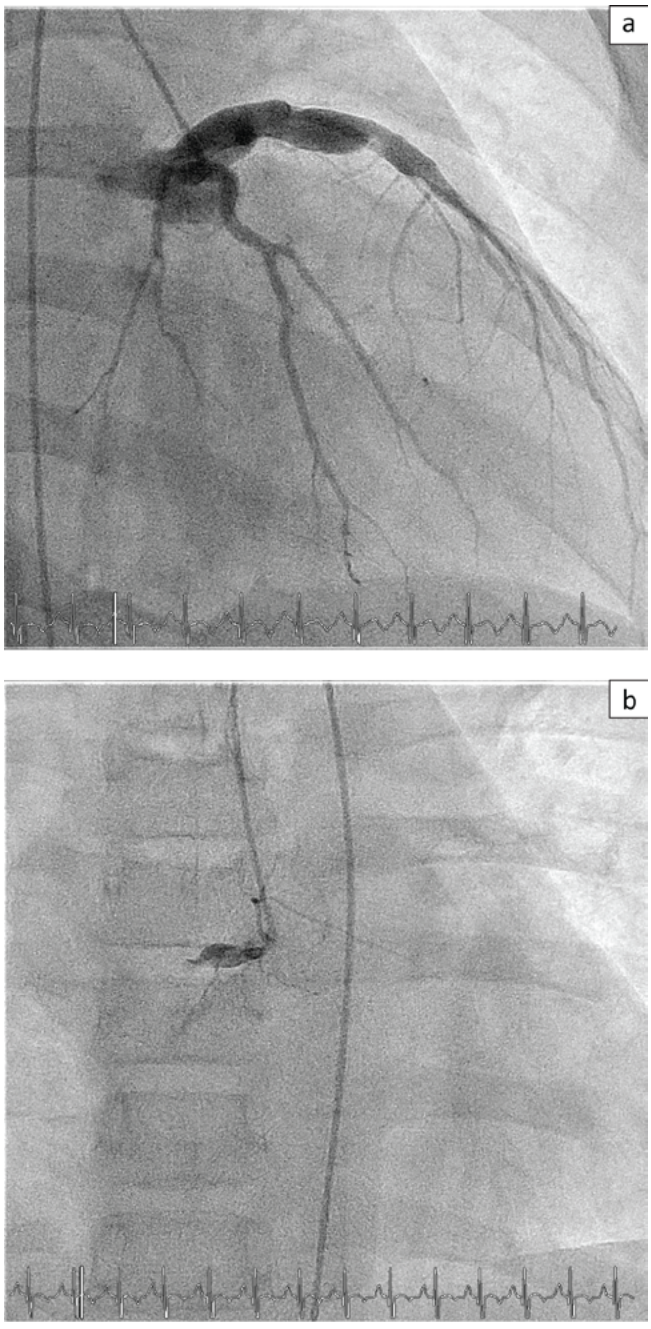

Figure 1. *Panel A*. Selective coronary angiography of the left and right coronary arteries. *Panel B*. The left coronary artery shows moderate aneurysmatic dilatation of the left anterior descending artery. The right coronary artery is completely occluded (both in strict a. p. 0° projection).

and hypokinesia of the posterior wall.

Subsequent coronary angiography showed a left coronary artery with formation of a moderate sized aneurysm, with preserved patency and no intracoronary thrombus formation. The RCA however was completely occluded (Figure 1A and B). We immediately attempted to revascularize the presumably thrombosed RCA. A 0.0018″ coronary guide wire (SV-8, Cordis) was repeatedly advanced into the ostium of the RCA and could be advanced several millimeters. Thereafter, intracoronary thrombolysis was started with tissue-plasminogen activator (rT-PA) injections at aliquot doses of 1–2 mg. This led to partial thrombolysis and improved visualization of the RCA, showing a large aneurysm filled with thrombotic material (Figure 2A and B). Repetitive direct intracoronary thrombolysis in combination with mechanical thrombus fragmentation using the guide wire and direct thrombus aspiration over the 6 F coronary guide catheter finally resulted in complete visualization of the RCA (Figure 2C), revealing two large aneurysms in combination with two severe stenoses with a diameter of less than 1 mm between them. The stenoses were dilated with a 3-mm coronary balloon (Savy, Cordis) at a maximum pressure of 6 atmospheres to improve coronary perfusion (Figure 2D and E). After a total dose of 20 mg intracoronary rT-PA, complete reperfusion of the RCA was achieved (Figure 2F). After complete revascularization, the exact anatomy of the RCA became evident, showing two giant aneurysms combined with severe stenosis (Figure 3). A coronary stent was not used due to the anatomy of the RCA, to avoid both malpositioning of the stent in the aneurysm and the risk of acute secondary thrombotic occlusion. The patient was transferred to the PCICU, and a combination therapy of clopidogrel (75 mg), acetylsalicylic acid (100 mg), and heparinization was administered for the subsequent three days. Control echocardiography on days 2 and 3 confirmed full recovery of the ventricular function. Troponin I levels decreased to normal (Figure 4). A scheduled recatheterization 3 days later showed complete and full restoration of coronary perfusion. The ECG normalized, showing normal function of the left ventricle without dyskinetic areas or apparent scarring. The patient recovered completely and was discharged with a combination therapy of acetylsalicylic acid and warfarin (target INR between 2.0 and 3.0). Planned control catheter evaluations after 6 and 12 months revealed excellent cardiac function and a patent RCA without new thrombus formation.

Despite an initial lack of evidence, the child's past medical history revealed a possible diagnosis of untreated atypical KD 6 months previously. He presented to another hospital with acute febrile illness for about 2 weeks, but with no signs of conjunctivitis, rash, mucosal changes, or lymphadenopathy. After 2 weeks, the fever disappeared and desquamation of the palms was visible. Echocardiography performed on days 4 and 10 of the illness was unremarkable. Follow-up echocardiography was advised, but the patient did not present to a pediatric cardiologist for follow-up examination.

Discussion

KD is one of the most important causes of acute coronary syndrome in young adults. About 5% of all patients with KD develop ischemic heart disease during long-term follow up, which is often associated with calcified stenosis [4, 5]. Catheter intervention is now established as a first-line therapeutic strategy for adult patients with coronary artery disease, and has provided satisfactory therapeutic results [6]. However, in adult as well as pediatric patients with KD, limited experience with catheter interventions has been reported [4, 7, 8]. Options for coronary revascularization in KD generally consist of intravenous coronary thrombolysis, percutaneous coronary intervention, or coronary artery bypass grafting [9, 10, 11, 12]. The guidelines for catheter interventions in KD, published by the research committee of the Japanese Ministry of Health, Labor, and Welfare, indicate that patients with acute myocardial infarction after KD can be candidates for percutaneous transluminal coronary revascularization and intravenous thrombolysis, patients with stenotic lesions with mild calcification can be candidates for percutaneous transluminal coronary balloon angioplasty (PCBA), and patients with severe calcifications can be candidates for rotational ablation [13].

Primary percutaneous coronary interventions in children presenting with clinical symptoms of acute myocardial infarction due to the sequelae of KD have been extremely limited and restricted primarily to

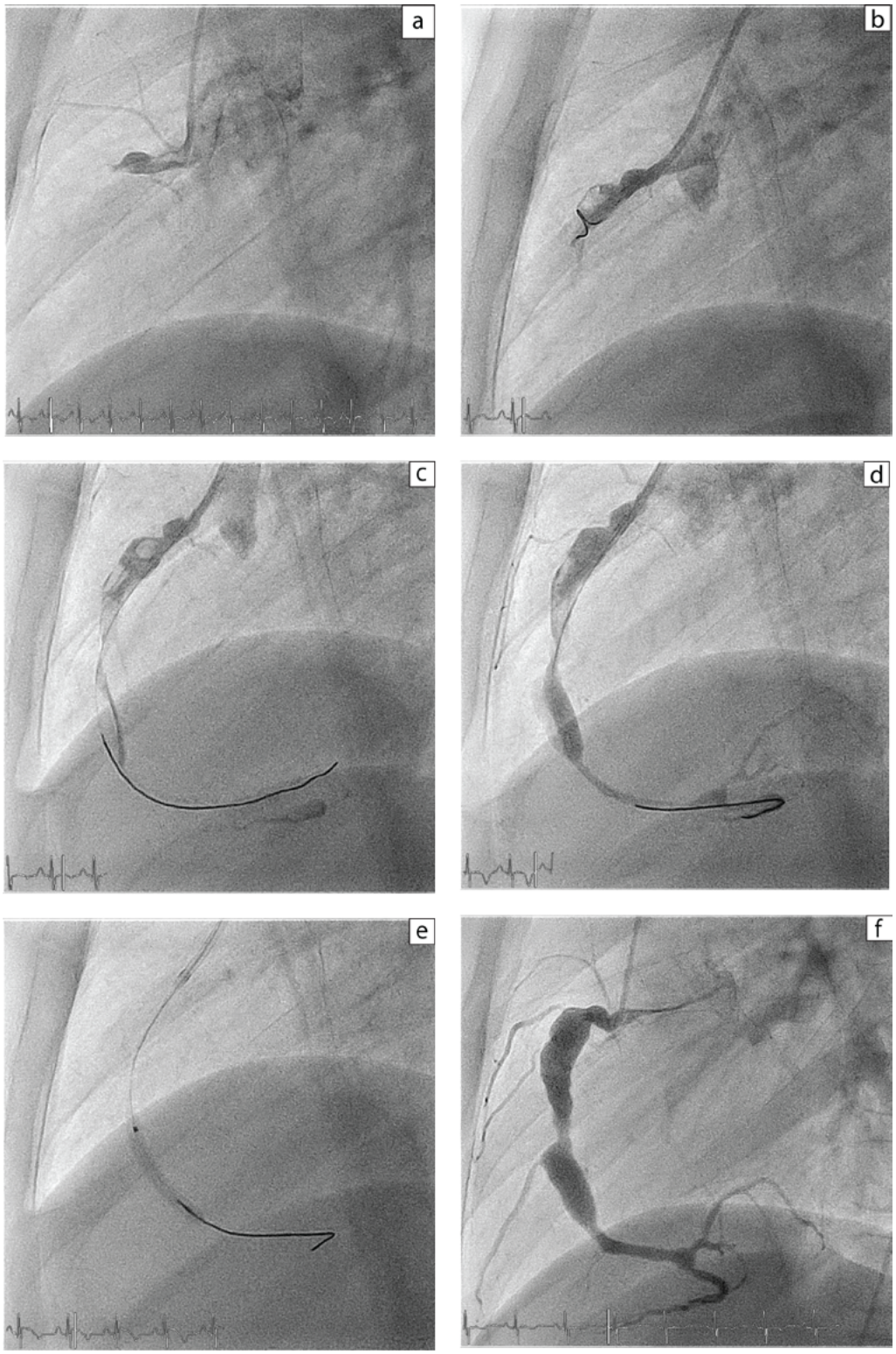

Figure 2. *Panel A.* Selective coronary angiography of the right coronary artery. *Panel B.* Complete occlusion. *Panel C.* Mechanical recanalization. *Panel D.* Local lysis. *Panel E.* Thrombus aspiration. *Panel F.* Balloon dilatation of the distal stenosis (all strict lateral 90° projection).

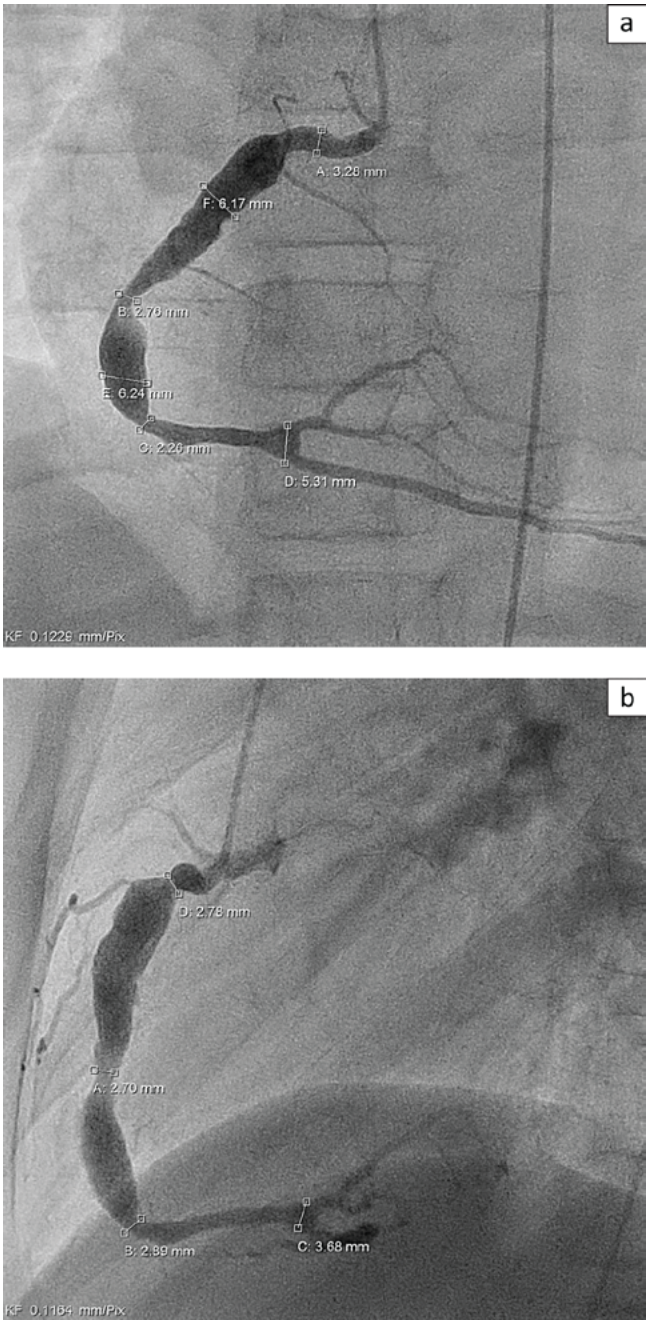

Figure 3. Selective coronary angiography of the right coronary artery (RCA) after complete revascularization *Panel A*. Frontal view. *Panel B*. Lateral view. The RCA shows two gigantic aneurysms measuring more than 6 mm in diameter. After dilatation mild stenosis at the exits of the aneurysms persists.

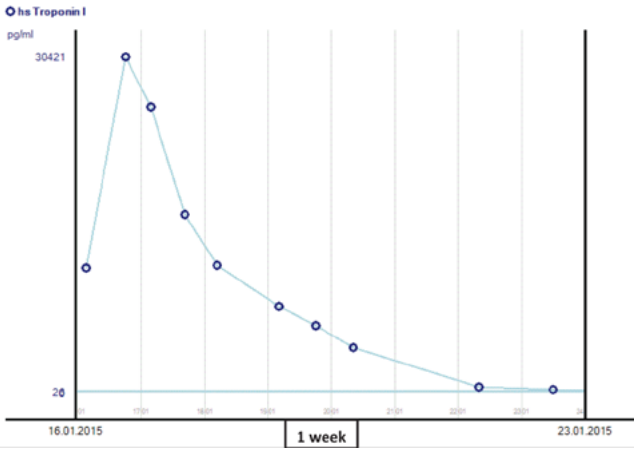

Figure 4. Levels of troponin I after revascularization of the right coronary artery.

cases from Japan and other Asian countries. Thrombolytic agents such as urokinase and rT-PA have been used to treat acute myocardial ischemia secondary to thrombus formation in CAAs of patients with KD [5, 10, 14]. Improved outcome was reported when the agents were administered directly into the coronary arteries [5, 15]. Ariyoshi et al. [4] reported three cases, in patients aged 20–35 years, in whom primary percutaneous coronary interventions in combination with intracoronary thrombolysis proved to be safe and effective in acute myocardial infarction. Karia et al. [14] reported a 29-day-old child with KD who presented with multiple medium-size CAAs as well as coronary thromboses, myocardial ischemia, and congestive heart failure. The infant successfully underwent intracoronary infusion of rT-PA. He had a history of KD at the age of 8 days. Mongiovi et al. [16] reported a 7-year-old boy with acute myocardial infarction in whom primary recanalization with angioplasty and complete reperfusion of the occluded artery was achieved. At 2-year follow up, ventricular function was still normal. Inaba used pulse infusion of thrombolysis (rT-PA) into the thrombus in a 24-year-old man with complete distal thrombosis of the RCA [15].

Interventional treatment in addition to thrombolysis was described in some other studies. Akagi et al. [3] reported the results of a nationwide review of 55 institutions in Japan: In 57 patients, percutaneous transluminal angioplasty (PTCA) was performed in 34, percutaneous transluminal coronary rotational ablation (PTCRA) in 13, directional coronary atherectomy (DCA) in 4, and stent implantation in 7. The success rate was 74% for PTCA, 100% for PTCRA, 100% for DCA, and 86% for stents. Ishii et al. [13] reported a

case series of 23 stenotic lesions in 22 patients (aged 2 to 24 years) where a total of 21 lesions (91%) could be treated successfully by PTCA, PTCRA, and stent implantation. In general, localized stenosis of the coronary arteries can be treated by balloon angioplasty, and in those patients with severe calcification, PTCRA is the treatment of choice with good short-term results [16–19]. Drossner et al. [20] reported a 3-year-old girl with acute myocardial infarction and large left and RCA aneurysms who had been diagnosed with KD at 4 months of age. Successful coronary revascularization was performed by balloon angioplasty and placement of two stents. Dahdah et al. [21] reported an 11 ½-year-old girl in whom successful recanalization was achieved using a high-frequency mechanical vibration catheter (Crosser catheter); additional balloon dilatation was performed and a stent was deployed. Finally, Parsa et al. [7] reported a 35-year-old man with acute myocardial infarction after a history of KD at the age of 5 years. The patient underwent thrombectomy and a stent was deployed. Grade III flow was established.

Rarely, covered stents may be needed to cover large aneurysms prone to intracoronary thrombus formation. Waki et al. [22] reported satisfactory long-term outcome for transcatheter polytetrafluoroethylene-covered stent implantation in a giant CAAs with a 90% stenosis.

In our case, we used a combination of the treatment modalities outlined above. First, mechanical thrombus fragmentation was performed, and direct intracoronary thrombolysis using high doses of rT-PA supported delineation of the vessel. Thrombus aspiration thereafter, in combination with additional local thrombolysis, outlined the exact anatomy of the RCA with large aneurysms and two severe stenoses, so that finally recanalization and complete reperfusion of the occluded RCA could be achieved by a combination of thrombectomy, intracoronary thrombolysis, and additional balloon angioplasty. PTCRA and DCA were not necessary due to the apparent lack of calcification.

Conclusions

Based on our experience and the literature presented, percutaneous coronary intervention is a safe and effective short-term treatment for children with acute myocardial infarction due to coronary sequelae of KD. The combination of various techniques may be necessary to address the different coronary pathologies as outlined in our case report.

Acknowledgments

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Conflict of Interest

The authors have no conflicts of interest relevant to this publication.

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Migraine Reduction After Transcatheter Closure of Interatrial Septal Defects: Another Brick in the Wall?

Migraine Reduction after ASD Closure

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Key Words

Migraine • Interatrial septal defects

Migraine is one of the most common medical diagnoses, affecting 13% of adult population, or 1 in 4 households, in the U.S [1]. Migraines frequently occur between 25 and 55 years of age, resulting in major limitations on quality of life and economic opportunity during our most generative years of life. The societal and economical implications include 112 million bedridden days per year and costs exceeding over $15 billion due to work loss [2]. Despite their prevalence and burden, migraines remain a sorely underdiagnosed and undertreated disability [1].

In Wilmhurst and colleagues' seminal trial [3], migraine relief was a serendipitous finding in select patients who underwent patent foramen ovale (PFO) closure for decompression illness and stroke. Similar findings in multiple retrospective cohorts [4-6] spurred the field to focus its sights on PFO closure in the setting of cryptogenic stroke.

A provocative, albeit opaque, relationship emerged between right-to-left shunt (RLS), migraines, and PFO closure. Cryptogenic stroke patients were twice as likely to have a history of migraine headaches as those without PFO (27% versus 14%, respectively) [7]. PFO was seen more frequently in people with migraine with aura than in age- and sex-matched controls (47% versus 17%, respectively) [8]. Headache activation after atrial septal defect (ASD) closure, specifically with Nitinol-based devices (Amplatzer), was reported, encouraging further investigation [9, 10]. All that was necessary was a prospective clinical trial, designed to account for the placebo effect and adjudicated by migraine neurologists: the Migraine Intervention with StarFlex Technology (MIST) trial [11].

Many interventional cardiologists were optimistic; we saw dramatic life changes in our patients. Otherwise healthy individuals with cryptogenic stroke who were debilitated, not by residual neurological defects, but by crippling migraine headaches, returned to our clinics months later reporting life-altering improvements in headache frequency and severity.

The construct collapsed with a negative trial, critiqued for its design, operators, patient selection, marginally effective device, and overreaching endpoint. Perhaps we should have predicted the study outcome based solely on the ubiquitous nature of headache. We did not have a pathologic footprint to track, which remains true to this day. It was known that migraine is an elusive target for phar-

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macological therapy; this held true for devices as well. These challenges culminated in the termination of MIST II.

Despite these setbacks, investigators have continued to explore the closure of interatrial septal defects and migraine relief. The study by Tayaka and colleagues [12] provides another link between the presence of RLS and migraines. Their data support the reports of a higher prevalence (56%) of migraines in patients with RLS, but also suggest a high prevalence in patients with ASDs (29%). While not an entirely novel finding, the relationship behind ASD and migraines has not been the emphasis of investigation. This prospective trial adds little to the body of evidence of nonrandomized PFO closure and migraine relief, but it demonstrates that there is potentially an interaction with ASDs, and their closure may impact headaches.

The study by Tayaka et al addresses several gaps of previous trials. The endpoint assessment of headache was based, correctly, on a neurologist's evaluation. The four-category reporting system for headache severity and frequency provides quantification consistent with the real world expectation of improvement. Follow-up was well documented, along with the response to clopidogrel, which may play a role in migraine relief. Notably, relief persisted beyond the termination of clopidogrel at 1 month.

The trial exhibits well-described limitations of nonrandomized clinical studies without control groups or blinding. The assessment of pharmacologic therapy for migraine headache was not described, and the evaluation tools did not include a headache diary. These omissions are especially important given that improvement, and specifically complete resolution, of migraines was high in all patients. Migraine relief was highest in patients after PFO closure but also high after ASD closure, with 15 of 20 patients improving and nearly half of these patients reporting complete resolution. The mean post-procedure follow-up for patients after ASD closure was half of that after PFO closure (22 versus 44 months, respectively). A longer follow-up period overall may have decreased the likelihood that relief was due to placebo and would have been beneficial to evaluate the underlying relationship between RLS and headache.

Tayaka and colleagues did not specify key methods and procedures, including the imaging protocol for evaluating interatrial septal defect anatomy and RLS. Thus, procedural success was not defined. Related procedural results were undescribed, namely the presence and quantitation of post-procedural residual shunt in patients after ASD closure, particularly in those without improvement of migraine. These descriptions and data are critical to correlating closure with relief, and particularly essential in the study of a clinical syndrome with placebo effects that may exceed 20% [13].

A large, randomized clinical trial aimed to overcome these limitations and provide a definitive foundation for evidence-based PFO closure for migraine headache. The Prospective, Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects with Migraine and PFO Using the Amplatzer PFO Occluder to Medical Management (PREMIUM) trial was presented in June 2015 at the American Headache Society [14]. PREMIUM was the third trial to examine migraine relief with PFO closure, the second to use the Amplatzer device, and the second to use sham surgery as a control. The primary endpoint of 50% reduction in migraine was not met; there was no difference in migraine attack frequency in patients who underwent closure ($n = 117$) versus patients randomized to sham and medical therapy ($n = 103$). Among migraineurs with aura, however, those in the closure group had a higher rate of complete remission than those in the sham group (10.8% versus 1.5%, $p = 0.02$).

These results are consistent with the compelling body of literature demonstrating migraine relief after PFO closure in the subset of patients who have migraine with aura. The high frequency of large RLS in these patients [8], and the high rate of migraine relief and even complete remission in patients after PFO closure [12, 14], suggest that RLS has a role in migraine pathogenesis. However, study findings must be cautiously interpreted before changing clinical practice. Currently, there are no studies actively enrolling for PFO closure in patients with headache, and it is purported that the U.S. Food & Drug Administration may want another trial. Fundamental questions for future investigation remain.

- In the absence of a pathologic signature, can we refine

our study group in subsequent randomized trials?

- Based on the safety of PFO devices [15], is it reasonable to address a cohort with headaches less recalcitrant than migraine?
- Can we define a PFO or RLS headache? Are there other substrates lacking chemical conversion by the pulmonary circulation in these patients?

In conclusion, Tayaka and colleagues have deepened our knowledge base. However, investigators must expand our inquiry to the basic science linking right-to-left circulation and headaches. Migraines are one of the most debilitating diseases, and, if a safe and simple cardiac procedure is to be provided in hopes of improving our patient's health and quality of life in their prime, it is imperative that we cement the construct between migraine, RLS, and this therapy.

Conflict of Interest

The authors have no conflict of interest relevant to this publication.

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