Transcatheter closure of perimembranous ventricular septal defects

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The isolated perimembranous ventricular septal defect is one of the most common congenital cardiac malformations. Although surgery has been performed and has a low associated risk, it still involves morbidity due to factors such as residual leaks, atrioventricular block, postpericardiotomy syndrome and arrhythmias. It has been speculated that percutaneous closure of these defects could minimize such complications. Recently, a device designed specifically for perimembranous ventricular septal defect closure, the Amplatzer membranous ventricular septal defect occluder, has been developed. Initial clinical experience with this device has been very encouraging with results showing a high rate of complete closure and a low incidence of complications at mid-term follow-up. In this article, the authors review their own and others’ experience with this device.


Introduction
The isolated ventricular septal defect (VSD) is one of the most common congenital cardiac malformations, accounting for approximately 20% of all lesions [1-4]. In 80% of cases, these defects occur in the area of the membranous septum [1-4], being in the outlet portion of the left ventricle immediately beneath the aortic valve and between the inlet and outlet portions of the right ventricle [5]. They are termed perimembranous (PM) defects and have variable extension to the adjacent muscular tissue of the inlet, muscular or outlet septum [1-4]. Their hallmark is a fibrous continuity between the tricuspid and aortic valve [1]. Minor associated abnormalities of the tricuspid valve may take the form of extra septal leaflet tissue or pouches that can partially or completely occlude the defect [1]. These pouches have also been called aneurysms of the ventricular septum, although they are not true septal aneurysms [1].

Restrictive VSDs
The PM VSDs may be classified according to their hemodynamic pathophysiology [2]. The degree of shunting across a PM VSD is determined by the size of the defect and the relative resistance in the systemic and pulmonary vascular beds [2]. Since most VSDs are oval, the maximal diameter of the defect can sometimes be misleading [6]. Nevertheless, the maximal VSD diameter is generally used and compared with the size of the aortic root in order to estimate the hemodynamic burden on the left ventricle, and the associated risk of pulmonary hypertension [1-4]. A defect is generally considered small when the orifice area is approximately 0.8 cm²/m² of body surface area [1], or when its diameter is less than a third of the size of the aortic root [1]. However, there is little scientific data to support this [1]. In the case of a small defect, there is usually a significant systolic pressure gradient between the left and right ventricles. These defects are also termed restrictive because the amount of pulmonary blood flow is solely determined by the size of the defect, assuming pulmonary vascular resistance is normal. In this case, indexed left ventricular end diastolic dimension for body surface area will be within the normal limits.
or slightly increased. Classically, children with these defects are asymptomatic and have excellent long-term prognosis [5]. Neither medical therapy nor surgery is usually indicated [1-6]. They should receive antibiotic prophylaxis against endocarditis when undergoing procedures likely to produce bacteremia [1-7]. Spontaneous closure of these defects has been reported in up to 80% of cases, and usually occurs during the first 5 years of life [1-3]. Some, however, suggest that even small defects, initially regarded as ‘nonsignificant’, may not have such a benign long-term course [8].

Nonrestrictive VSDs
At the other end of the spectrum, nonrestrictive VSDs occur when the size of the defect is larger than 50% of the size of the aortic root [4]. In practice, the judgement of the size of a nonrestrictive VSD is better made on hemodynamic grounds [1]. In other words, when right and left ventricular systolic pressures are equal, and the amount of pulmonary blood flow is solely determined by pulmonary vascular resistance [2]. Since pulmonary circulation is subjected to increased flow at systemic levels of pressure early in the course of the disease, children with these defects are at risk of developing irreversible pulmonary vascular changes within the first or second year of life. Surgical treatment should not be delayed in these patients [8].

Moderately restrictive VSDs
Moderately restrictive VSDs show defects that are approximately 30 to 50% of the size of the aortic root [4], with a variable pressure gradient between the left and the right ventricles. The right ventricular systolic pressure is increased, usually remaining under 50% of systemic levels, and the pulmonary vascular resistance is higher than normal [1,3]. The degree of left-to-right shunting is moderate to severe in infancy, following the progressive fall in pulmonary vascular resistance that occurs after the neonatal period [1-3]. These defects are associated with left atrial and left ventricular dilatation due to volume overload. The amount of pulmonary blood flow is determined both by the size of the defect and the pulmonary vascular resistance [2]. If children with moderate PM VSDs develop symptomatic congestive heart failure with clinical manifestation of pulmonary overcirculation, a trial of medical therapy is indicated [1,9]. Medical management may temporarily improve symptoms and allow time for spontaneous closure of the VSD. However, if these children present with intractable congestive heart failure despite maximal medical therapy or, more commonly, failure to thrive or recurrent pulmonary infections, treatment is indicated to prevent pulmonary vascular disease [1-3,6,9].

Surgical closure of PM VSDs
Surgical closure of PM VSDs has been performed safely with a very low mortality rate, although complications, such as residual leaks, atrioventricular block, postpericardiotomy syndrome and arrhythmias have been well described [3]. Therefore, as an alternative approach to surgery, transcatheter closure of PM VSDs has been attempted using a variety of occluding devices, such as the Rashkind double-umbrella (RUD), the buttoned device and coils [10-15]. However, results with these devices have been suboptimal because they were not specifically designed for this purpose, and therefore none has gained wide acceptance. Large delivery sheaths, inability to recapture and reposition, structural failure, dislodgement and embolization of the device, interference with the aortic valve resulting in aortic insufficiency and a high rate of residual shunting are the major limitations of the previously described techniques [10-15].

After successful use of the muscular VSD device from AGA Medical Corporation (MN, USA) [9,16-22], the Amplatzer membranous VSD occluder (AVSO), a device designed specifically for PM VSD closure has been developed [23]. Initial clinical experience with this new device has been very encouraging [24-27]. In this review, the authors discuss the feasibility, safety and efficacy of transcatheter closure of PM VSDs with the AVSO, reporting further experience derived from the authors’ institutions.

Device & delivery system
The device
The AVSO consists of two low-profile discs of a self-expandable Nitinol wire mesh connected by a very short (1.5 mm) cylindrical waist [24-27]. The waist has a diameter ranging from 4 to 18 mm with 2 mm increments. Although the discs are parallel, they are offset to provide a minimal subaortic rim: the left disc is 0.5 mm larger than the waist at its superior aspect and 5.5 mm larger at the inferior aspect (FIGURE 1). A platinum marker band is laser-welded to the inferior portion of the larger part of the left ventricular disc for orientation (FIGURES 1 & 2), pointing to the left ventricular apex during implantation. The right ventricular disc is centric, being

Figure 1. The Amplatzer membranous VSD occluder. On the left side, the device is seen in profile. The left disc is acentric and connected to the right disc by a short cylindrical waist. The delivery cable is screwed to a female microscrew on the right disc. On the right side, the device is seen from the front. Polyester patches are sewn to the thin Nitinol wire mesh.
4 mm larger than the waist (FIGURE 1). Reinforced layers of polyester patches are sewn to the Nitinol wire mesh to increase thrombogenicity. The device connects to the delivery system by a female microscrew, located in the central portion of the right ventricular disc. This screw is somewhat longer than the ones found in the other Amplatzer devices and has a flat shape on its superior aspect. Therefore, the flat portion of the microscrew on the right side and the platinum marker on the left side are found in opposite locations, in a superior-inferior fashion (FIGURE 2) [24–27].

The delivery system

The delivery system is a coaxial one, consisting of a delivery cable, a pusher, a rotational plastic vise, a plastic loader with a detachable hemostatic valve and a side arm and a long braided sheath with dilator [24–27]. The delivery cable is somewhat thinner and flloppier than other Amplatzer cables used for patent ductus arteriosus (PDA) and atrial septal defect (ASD) occlusion. The pusher has a metallic capsule at its end designed to fit the microscrew of the device, with a flat part located at its superior portion (FIGURE 2). In addition, the pusher has a right curve (180°), matching the curvature of the long sheath. The sheath is braided in order to avoid kinking during manipulation (TorqVue, AGA) and has a 180° curve at its distal segment (Mullins type) to allow better positioning at the left ventricular apex. The sheaths are available in 6 Fr (for a 4 mm device), 7 Fr (for 6 to 8 mm devices), 8 Fr (for 8 to 12 mm devices) and 9 Fr (for 14 to 18 mm devices) [24–27]. To load the device, the delivery cable is passed through the pusher and both are passed through the plastic loader with the attached hemostatic valve. The device is screwed to the male screw of the delivery cable by clockwise rotation. The delivery cable is pulled back allowing for the flat portion of the microscrew of the device to align with the flat portion of the metallic capsule of the pusher (FIGURE 2). This allows the device to be properly positioned with the upper flat part of the left ventricular disc toward the aortic valve during implantation [9]. This alignment may need some manual adjustment until a ‘click’ is heard or felt. To avoid disconnection between the device screw and the pusher, a gentle traction is applied to the delivery cable, which is then fixed in a proper position using a rotational plastic vise or a surgical clamp [9] close to the proximal end of the pusher [27]. In this way, the delivery cable and the pusher work as a unit when the latter is pulled or pushed. The device is loaded into the plastic loader under saline solution by gently pulling the pusher. To completely de-air the system, the device is further flushed inside the loader with saline injections through the side arm of the hemostatic valve.

Figure 2. Fitting the pusher to the device. The pusher has a metallic capsule at its end designed to fit the microscrew of the device. The flat portion of the metallic capsule of the pusher should align with the flat portion of the microscrew of the device. This allows the device to be properly positioned during implantation with the upper flat part of the left ventricular disc toward the aortic valve.

Figure 3. Left ventricular angiograms in long axial view. A: A large perimembranous ventricular septal defect measuring 9 mm. B: After the defect is retrogradally crossed, the rope wire is advanced to the left pulmonary artery. C: The rope wire is snared and exteriorized from the femoral vein. D: The long sheath and dilator are advanced from the vein until they touch the retrograde catheter that was left in the inferior vena cava ("kissing catheters"). E: After the long sheath reaches the ascending aorta, the dilator is retracted inside the sheath and the rope wire is pushed to the left ventricle with the aid of the retrograde catheter. F: The dilator is advanced over the wire looped in the left ventricle reaching the apex followed by the sheath.
Animal studies

Like other Amplazer devices [22], the AVSO occluder underwent extensive animal studies and achieved very good results [23]. After these studies were reported, the device underwent further improvements in its design and delivery system before it was first used in humans.

Trials in humans

The initial trials in humans were carried out after approval of the protocols by the local ethics committees at different centers in the world. Informed consent for the procedure was obtained from the patients or their guardians.

Patient selection

Treatment of PM VSDs has been classically indicated in the presence of significant left-to-right shunt resulting in left ventricular volume overload, usually determined by the presence of cardiomegaly on chest radiograph or by transthoracic echocardiography [19]. Since infants with large-size PM VSDs usually present with signs and symptoms of congestive heart failure and failure to thrive, surgical repair is generally carried out within the first few months of life [19]. Patients with moderate-size, somewhat restrictive PM VSDs that can be managed medically are considered candidates for device closure once they attain approximately 8 to 10 kg in weight [19]. It has been widely accepted that small PM VSDs do not impose any volume overload on the left ventricle and are not associated with pulmonary vascular complications [20]. Therefore, closure of such defects has not been usually advised and endocarditis prophylaxis is the only recommendation [20]. However, recent evidence suggests that the small VSDs may not be so benign in the long term [8]. Increased morbidity and mortality may ensue due to arrhythmia, cardiac failure and endocarditis [8]. Therefore, close follow-up is mandatory in patients with small VSDs. The authors believe that there are certain cases where patients with restrictive defects should be considered for closure on an individual basis:

- Failure to thrive unrelated to other diseases
- Recurrent pulmonary infections
- Frequent wheezing episodes leading to visits to the emergency department, sometimes requiring hospitalization
- Progressive increase in left ventricular end diastolic diameter
- Development of ventricular arrhythmias

Furthermore, in developing countries, especially in rural areas, where access to medical attention may be suboptimal precluding close follow-up, closure of such defects should also be considered. Since surgical closure does not eliminate the chance of contracting endocarditis, and may even initiate it [7], avoidance of this complication cannot be an indication for surgical intervention [11]. It is not yet known whether closure of VSDs using the AVSO eliminates the risk of endocarditis. On the other hand, a previous episode of endocarditis is generally regarded as an indication for closure, irrespective of the size of the VSD [3].

Echocardiography

Two-dimensional transthoracic echocardiography (TTE) with Doppler techniques plays an important role in selecting patients for device closure. Standard views are used to delineate the size and location of the PM VSDs, chamber sizes and function, associated abnormalities and aortic valve function [9]. The distance from the aortic valve is recorded and, in this regard, the presence of a 2 mm or more rim of tissue between the defect and the aortic valve is generally considered to be a prerequisite for device closure of PM VSDs [9]. Although TTE is an important tool for selection of patients for device closure, transesophageal echocardiography (TEE) is generally employed to guide device implantation during the procedure. However, TTE, TEE and also intracardiac echocardiography can all be used to monitor adequate device placement as long as excellent images are obtained [24].

Figure 4. Left ventricular angiograms. A: After the wire is removed, a 10 mm device is advanced through the long sheath. B: The left disc is deployed in the left ventricle and the whole system is pulled back towards the septum. The marker is pointing downwards. C: The waist and the right disc are deployed across the defect. D: Repeat angiogram before release confirms good device position. E: Small residual shunt is observed through the device after release. Left ventricular dilatation is conspicuous in this diastolic frame. F: Aortic angiogram in mid-left anterior oblique view demonstrating the distance between the device and the aortic valve, and no aortic insufficiency.
Procedure protocol

The procedure is preferably performed under general endotracheal anesthesia with continuous TEE guidance [9]. Femoral artery and vein access are obtained and a 4 to 5 Fr and a 6 to 7 Fr sheath inserted. Heparin sulfate (150 IU/kg; maximum: 10,000 IU) is given. Standard right and left heart catheterization is carried out and a left ventricular angiogram obtained in the long axial oblique view. Angiograms in the aortic root in shallow left anterior oblique view and in the left ventricle in the hepatocaval view are also obtained as judged necessary. A marked pig-tail catheter (Royal-flush; Cook Cardiology, IN, USA) is left in the inferior vena cava (IVC) or on the chest for calibration purposes [21]. The defect is measured at the end of diastole in the view which affords the best profile. TEE is used to reassess anatomical and functional parameters. The most important steps in the protocol are demonstrated in Figures 3A & 5, and are described below [9].

Crossing the VSD from the left ventricle

The VSD is crossed in a retrograde fashion using a 4 or 5 Fr right coronary Judkins catheter ( Cordis Corporation, FL, USA) with the aid of a hydrophilic guide wire (Roadrunner, Cook Cardiology). After crossing the defect, the catheter is left at the apex of the right ventricle and the hydrophilic wire exchanged for a soft and flexible 0.035 inch diameter, 300 cm long wire (Rope wire, AGA), which is then maneuvered to the left pulmonary artery [23].

Snaring the rope wire

The wire is snared in the left pulmonary artery using a goose neck snare (Microvena, MN, USA) and exteriorized via the right femoral vein to establish a stable arteriovenous loop. The retrograde catheter across the VSD follows the exchange wire, being left at the junction of the IVC and the right atrium (RA). To ensure free passage of wires, catheters and sheaths across the tricuspid valve, a 7 Fr endhole Berman wedge catheter (Arrow International, PA, USA) is initially used to reach the left pulmonary artery, being subsequently exchanged for a 6 Fr therapeutic right coronary Judkins catheter (Medtronic Incorporation) for the snaring maneuver [27].

Device selection

The device is selected to be 1 to 2 mm larger than the VSD size [34-27], estimated by both TEE and angiography using the minimal defect diameter on the left ventricular side in diastole [27]. In patients with aneurysm-like formations, especially in the setting of multiple or small exit holes, device selection is not as straightforward [27]. One must take into account the size of the VSD on both sides of the ventricular septum to avoid the development of a 'mushrooming' effect on the device. Generally, in the setting of aneurysm-like formations, slightly oversized devices are selected to keep the left disc in alignment with the muscular septum with the remaining portions of the device filling the aneurismal sac.
Delivery sheath progression

The appropriate sized long sheath and dilator are advanced from the femoral vein until the tip of the dilator touches the tip of the retrograde catheter in the IVC–RA junction (the "kissing catheter" technique) [27]. The arteriovenous loop is tightened by pulling the wire on both sides of the system and fixing its position using surgical clamps at the end of the arterial catheter and the venous sheath. The long sheath is advanced from the femoral vein to the ascending aorta across the VSD by gently pulling the arterial catheter and pushing the sheath. Once the sheath reaches the ascending aorta, the surgical clamps are released, the dilator is retracted a few centimeters inside the sheath and the arterial catheter exchanged for a more rigid 5 Fr therapeutic right coronary Judkins catheter (Medtronic). After loosening the wire loop, the sheath is pulled slowly until the tip reaches the aortic valve. The wire is then pushed from the arterial side to form a curve in the ascending aorta, then to cross the aortic valve and enter the left ventricle. The arterial catheter is also pushed to provide more support for the wire loop to cross the valve and reach the body of the left ventricle. This maneuver in turn pushes the sheath towards the left ventricle, just below the aortic valve. The dilator is advanced over the wire, reaching the left ventricular apex, followed by the sheath. The dilator is removed and a repeat left ventricular angiogram is obtained through the side arm of the long sheath to further assess the VSD morphology. The exchange wire is withdrawn from either the artery or the vein [27].

Deployment of the device

After the device is loaded, it is advanced until it reaches the tip of the sheath. The left ventricular disc is deployed in the mid-ventricular cavity after the sheath is pulled away from the apex, by gently pulling the sheath and pushing the pusher [24–27]. Due to the alignment of the flat portions of the device microcatheter and the metallic capsule of the pusher, the device invariably exits the sheath in the correct orientation (i.e., with the platinum marker in the larger part of the left disc, pointing downwards towards the left ventricular apex) [26–27]. At this point, TEE is essential to make sure that the mitral valve apparatus is not entangled with the left ventricular disc [29]. After deployment of the left disc, the sheath and the pusher are pulled as a unit until the left disc (almost) touches the left ventricular septum. The connecting waist and the right disc are best deployed by advancing the pusher catheter while keeping gentle tension on the delivery sheath. The device will shorten as it expands. If the right disc is uncovered by withdrawing the sheath it may pull through the defect or entangle the tricuspid valve.

Adequate positioning and orientation of the device are confirmed by TEE and repeat angiograms. TEE is again essential to make sure that the tricuspid valve apparatus is not entangled with the right ventricular disc [29]. In smaller patients or in patients with defects restricted by extensive tricuspid valve tissue including aneurysm-like formations, it may be difficult or even impossible to position the tip of the sheath near the left ventricular apex. In these cases, experience suggests that positioning the tip of the delivery sheath in the descending aorta and advancing the device to the tip of the sheath in this position may mimic the downward curve of a left ventricular apex position. Device orientation may be correctly directed in this way. Another option is to partially deploy the left disc in the ascending aorta, assuming a 'bubble shape'. The whole system is gently pulled back towards the left ventricle across the aortic valve. Care must be taken not to damage the aortic valve and pull the device all the way through the defect. In the left ventricular outflow tract, the remaining portion of the left ventricular disc is then deployed. However, by doing so, the device may not exit the sheath in the correct orientation. If this should happen, it can be dealt with by deploying the entire device in the left ventricle and rotating the sheath and the delivery cable clockwise to make the platinum marker point downwards [27]. When the sheath cannot be positioned in the left ventricle, device implantation without the pusher may also be employed to optimize flexibility, facilitate device rotation if needed and to avoid tension on the system [MASURA, PERS. COMM.].

The final step is to detach the device, which can be accomplished by unscrewing the cable while the device microcatheter is engaged in the pusher catheter capsule. The microcatheter can be dislodged by advancing the delivery sheath over the pusher catheter while keeping gentle tension on the pusher catheter to avoid advancing the device. This has the advantage of avoiding rotational force on the device during unscrewing and the disadvantage of pushing against the device after deployment. Either technique appears to work. Once the device is released, the cable and pusher should be brought inside the sheath immediately to prevent any injury from the sharp end of the cable [29]. Repeat TEE and angiograms are performed to assess final device position and orientation, residual shunting and the functional status of the aortic, mitral and tricuspid valves. Cefazolin (20 mg/kg; Keftzol®; Eli Lilly and Co., IN, USA) is given during the procedure and at 8 h intervals (for a total of three doses). Hemostasis is achieved by manual compression. The patients are awakened in the catheterization laboratory and transferred to the recovery room for routine clinical observation. They are discharged the following day and instructed to receive aspirin (2–5 mg/kg/day; up to a maximum of 100 mg for 6 months), avoid contact sports for 1 to 2 months and observe the recommendations for endocarditis prophylaxis for 6 months or until complete closure has been documented. A chest radiograph, a 12 lead electrocardiogram and a TTE are obtained before discharge and scheduled after 1 to 3 months, 6 months, 12 months and yearly thereafter [27].

Results at the authors' institutions

Transcatheter closure of PM VSDs with the AVSO was attempted in 18 patients from December 2002 to December 2003. The results on the first ten patients have been presented as an abstract [28] and were included in a previous paper [27]. Median age was 8 yrs (range: 3–32), and median
through the long sheath before implantation, were seen in two of these patients. Defects shrouded by extensive tricuspid valve tissue but with no aneurysm formation were seen in six patients (Figure 6). A further four patients had defects with little or no adjacent tricuspid valve tissue and three patients had defects associated with prolapse of the right aortic cusp with one showing mild aortic insufficiency (Figure 7).

The authors had to change the size of the device for a larger one in two patients, one who had an aneurysm-like formation. In two patients, the sheaths kinked at the tricuspid valve/VSD level, prompting their removal. In three patients the authors were unable to position the sheath near the left ventricular apex, therefore partial opening of the left disc in the ascending aorta was required. In one of these cases the device was implanted without the pusher, as described above.

**Immediate complications**

Two patients developed atrioventricular block after the long sheath crossed the defect. In one patient, immediate recovery was observed after atropine administration. In the other patient, there was no response to drug therapy, and therefore ventricular pacing was required. The procedure was abandoned and sinus rhythm was restored after 4 h. One patient had transient bilateral brachial palsy due to the position of the arm during the procedure. In one patient who had an aneurysm-like formation with two exit holes, the device was implanted through an inferior hole and remained with the marker at 9–10 o’clock position despite many attempts at rotating the delivery system. However, because the left ventricular disc was covering the superior exit hole, and was still distant from the aortic valve, the device was released with complete closure and no aortic regurgitation. In the smaller patient included in this series (14 kg), the right ventricular disc was entangled with the tricuspid valve apparatus after its deployment, resulting in significant tricuspid stenosis (mean gradient of 11 mmHg) and significant right-to-left shunting across a patent foramen ovale, which persisted after the device was released from the delivery cable. The tricuspid valve apparatus was released from the right disc microcatheter using a gooseneck snare, resulting in immediate normalization of the tricuspid valve function and saturation levels. A ‘mushrooming’ effect on the device was seen in two patients, one of whom had a 17 mmHg gradient across the left ventricular outflow tract.

**Morphological & technical issues**

The authors found four basic patterns of PM VSD morphology. In five patients, the VSD was associated with aneurysm-like formations of the membranous septum with a ‘cauliflower’ appearance on angiography (Figure 6). Multiple exit holes on the right side of the aneurysm, which were only demonstrated after a repeat left ventricular angiogram was obtained weight was 22 kgs (range: 14–80). The mean ratio of pulmonary (Qp) to systemic (Qs) blood flow was 2.1 ± 1.3 (range: 1.5–5.5). The VSD diameter ranged from 3.5 to 10 mm (mean: 7.5 ± 1.5) as determined by TTE, from 3 to 17 mm (mean: 7.7 ± 4.2) by angiography and from 2.5 to 15.0 mm (mean 7.9 ± 3.9) by TEE. The mean waist diameter of the device was 10.5 ± 4.1 mm (range: 6–18 mm, median: 10). The fluoroscopy and procedure times were 38 ± 16 min (range: 16–58) and 120 ± 45 min (range: 63–210), respectively. One patient had undergone surgical repair of coarctation of the aorta in the neonatal period and also had a bicuspid aortic valve, a nonstenotic parachute mitral valve and a left ventricular infundibular fold. Successful implantation of the device was achieved in all but one patient.
Results available in the literature

Perhaps the largest published study of transcatheter closure of congenital VSDs was reported by Arora and colleagues from India [11], albeit with a limited number of patients specifically using the AVSO. Closure using various devices was attempted in 137 patients ranging from 3 to 33 years of age. The RUD was employed in 29 patients, the AVSO in 107 and a Detachable Coil in one. The VSD diameter ranged from 3 to 12 mm and the location was perimembranous in 91 patients and muscular trabecular in 46 patients. The procedure was successful in 130 (94.8%) patients, giving a success rate of 86.2% for the RUD and 97.1% for the AVSO. Residual shunt at 24 h was seen in eight (32%) patients with a RUD and in one patient (0.9%) with an AVSO. Transient bundle branch block was seen in three (2.8%) patients and two (1.9%) had complete heart block. New tricuspid stenosis and tricuspid regurgitation was observed in one patient each with an AVSO. After immediate balloon dilatation, the mean pressure gradient across the tricuspid valve decreased from 11 to 3 mmHg in the patient with tricuspid stenosis. In a mean follow-up of 55.2 ± 10.7 months, the device was in position in all patients. No one developed late conduction defect, atrioventricular block, infective endocarditis, or hemolysis. At 9-months follow-up, the mean pressure gradient across the tricuspid valve was 3 mmHg in the patient with tricuspid stenosis. Complete exclusion of the defect was achieved in 129 (99.2%) patients. One patient with a RUD had persistent residual shunt underwent a second procedure with an AVSO. In three out of 107 patients, the AVSO procedure was unsuccessful. In these patients, the defect was PM with a superior margin less than 5 mm from the aortic valve and the specially designed perimembranous AVSO had to be retrieved due to significant acute atrioventricular block resulting in hemodynamic compromise. The authors conclude that, in properly selected cases of perimembranous and muscular ventricular septal defects, transcatheter closure is safe and efficacious using appropriate devices. The success and occlusion rates are higher with the AVSO compared with other devices. Muscular defects also have higher success and occlusion rates than those that are perimembranous in location.

Two single-center studies with a small number of patients [24, 25], and one multi-center study on transcatheter closure of PM VSDs using the AVSO have been published recently [26]. In a paper by Hijazi and colleagues, six patients with PM VSDs underwent device closure [24]. Patients ranged in age from 3.5 to 19 years (median: 10.5 years) and in weight from 15 to

Immediate & follow-up results

Complete closure was seen in 12 patients immediately after device release and in all 17 patients after 3 to 6 months. There was no new tricuspid or aortic insufficiency either immediately after the procedure, or during follow-up. All patients, except one, were discharged the following day. In one patient with prolapse of the right coronary cusp and mild aortic insufficiency, the ratio of insufficient jet/aortic valve annulus increased from 0.10 to 0.15, which remained unchanged after 12 months. Mild peak instantaneous gradients (25 and 17 mmHg, respectively) across the left ventricular outflow tract at discharge were seen in two patients, but this normalized after 3 months. Left ventricular function was normal in all patients at discharge and during follow-up. A new right ventricular bundle branch block pattern was observed at discharge in one patient, which remained unchanged after 12 months. In another patient, a new left ventricular bundle branch block pattern was observed following a blunt chest trauma 4 months after device implantation. This patient was hospitalized for 5 days for clinical observation and a Holter study and an exercise test revealed sustained sinus rhythm and no further abnormalities. All patients were clinically well, asymptomatic, in sinus rhythm and on no medications in a mean follow-up of 9 ± 3 months. There was no episode of immediate or late device embolization and hemolysis.
45 kg (median: 29 kg). One patient with associated pulmonary
valve stenosis had shortness of breath. The median "Qp/"Qs ratio
was 1.6 (range: 1.1–3) and the median left ventricle end-diastolic
dimension (LVEDD) was 44 mm (range: 38–52 mm). The
devices were deployed via the femoral vein using 7 to 8 Fr
sheaths. There was immediate complete closure in all patients.
One patient developed trivial aortic regurgitation. There were
no other complications. The median fluoroscopy time was
15.5 min (range: 10.3–53.4 min). At 24 h, all patients were
doing well. The median LVEDD decreased to 38 mm
(range: 34–47 mm). One patient continued to have trace aortic
regurgitation. All patients were discharged after 24 h.

Thompson and colleagues reported the results of transcatheter
closure using the same device in ten children, aged 1.5 to
12 years, with small PM VSDs [29]. The prosthesis diameter was
chosen to be 1 to 2 mm larger than the largest diameter of the
defect. The device was delivered using a 7 to 8 Fr gauge sheath.
The PM VSD diameter ranged from 2 to 8 mm and the device
diameter ranged from 4 to 8 mm. After deployment of the
prosthesis there was no residual shunt in nine of the ten
patients (90%). In one patient there was a trivial residual
shunt that disappeared at the 3 month follow-up. Transient
complete left bundle branch block developed in three
patients. No other complications were observed.

In a multi-centric study, Bass and colleagues reported the
largest study using the AVSO available in the literature [30].
This report described the use of the device in 27 patients.
Implantation was successful in 25 (93%), with one removed for device-
related aortic insufficiency and inability to position the delivery
sheath in another. Device orientation was excellent when the
device was initially advanced through a standard delivery sheath
positioned in the left ventricular apex. Within 1 week, 23 had
complete occlusion (92%), with a tiny (< 2 mm) residual shunt in
the other two. In the 25 subjects with the device left in place,
device-related aortic or tricuspid insufficiency, arrhythmias and
embolization were not observed.

In another multi-center study, recently published as an
abstract [30], Holzer and colleagues reported the immediate and
follow-up results of catheter closure of PM VSDs using the
new device in 49 patients. The median age was 8.5 years
(range: 0.7–50 yr) and the median weight was 27.1 kg
(range: 7–121 kg). Prolapse of the aortic cusp with associated
regurgitation was present in two patients. The median size of
the VSD by TEE was 8 mm (range: 3–13 mm). The median
Qp/"Qs was 1.6:1 (range: 1–10). The device was implanted
successfully in 48 out of 49 patients. The median device size
used was 10 mm (range: ±16 mm). The median fluoroscopy
time was 21.5 minutes (range: 9.4–73.9 min). In five
patients, both discs were deployed but not released (n = 4) or
released in the left ventricle (n = 1) with successful recapture
or snare. No device-related left ventricular outflow tract
obstruction was observed. Complications encountered
included new aortic regurgitation in two patients (one resolved
by 6 months), both trivial to mild degree; hemolysis in one and
intermittent complete heart block requiring pacemaker in
another patient. The left ventricle left diastolic dimension
(LVEDD) decreased from 46 mm to 42 mm within 24 h of
closure. There were no procedure-related deaths. Immediately
after the procedure 26 patients had complete closure, 27 had
a trivial residual shunt and three patients had a small shunt. For
nine out of 20 patients, follow-up data at 6 months was
available, LVEDD was further reduced in eight patients; in all nine
patients the VSD was completely closed. No new complications
were encountered.

Discussion

Percutaneous closure of PM VSDs of different sizes and
morphologies with the AVSO was feasible, generally safe and
very effective in the authors' and others initial experiences
[24–29]. As observed with the use of other Amplatzer devices, this
new device has several advantageous features:

• It induces a high rate of complete closure
• The delivery system is simple and user friendly
• It requires a relatively low profile sheath for implantation
• It allows recapturing and repositioning if needed
• The short waist of the device obviates protrusion into both
ventricles and minimizes contact with the tricuspid valve
• Due to the anentric configuration of the left ventricular disc,
  it remains distant from the aortic valve without interfering in
  valve function

The authors believe that additional contrast media injections
performed through the long sheath or through the retrograde
catheter during device implantation were useful to delineate at
best those defects associated with an aneurysm-like formation,
especially in the setting of more than one exit hole on the right
side [27]. This diagnosis is important since it may have implications
in device selection and modification in the technique of
implantation. Moreover, it may be overlooked by TTE and TEE
and even by standard angiography. Selection of the size of the
device may not be straightforward in patients with aneurysm-like
formations. Oversizing did occur in two of the authors' patients,
resulting in a 'mushrooming' effect on the device and a gradient
across the left ventricular outflow tract in one patient. Even if one
measures the VSD at the crest of the septum and sticks to the
'true of thumb' to select a device 1 to 2 mm larger than the
defect, 'mushrooming' may still occur because the central waist of
the device is likely to be squeezed by the exit hole on the right
side. It is possible that dilation of a 'mushroomed' left ventricular
disc with a balloon dilation catheter could cause it to reconfigure.

Device elongation may theoretically be avoided if one leaves
the waist of the device straddling the crest of the septum and the
tight disc inside the aneurysm, avoiding pulling it all the way
towards the right ventricle across the exit hole. Whether this
approach may increase the chances of embolization is debatable.
On the other hand, no 'mushrooming' was observed in three of
the authors' patients with an aneurysm-like formation and just
one exit hole, in which the left ventricular disc was left inside the
aneurysm, with the waist straddling the exit hole. More data are
needed to establish solid guidelines for optimal device selection in patients with this morphologic pattern. Furthermore, device implantation may be difficult, and adequate device orientation may not be achieved in a multi-fenestrated aneurysm, especially when the sheath is crossing it through an inferior exit hole, as seen in one of the authors' patients. Although recrossing the defect through the superior exit hole might be required in some cases, releasing the device in the opposite orientation in the patient did not result in aortic valve dysfunction, since the defect was still distant from the aortic valve. However, longer follow-up on aortic valve function is needed before this is generally accepted. A mild gradient across the left ventricular outflow tract was also detected in another patient in the series and may be related to the presence of a left ventricular infundibular fold and a narrower subaortic region, since 'mushrooming' was not seen in that case. The gradient reduction observed in both patients after 3 months may be explained by progressive reduction in the device profile and reconfiguration, which is similar to what happens to the ASD Amplatz devices. For patients with no aneurysm-like formations, determination of the VSD size and selection of a device 1 to 2 mm larger than the defect was more straightforward, especially when there was little or no adjacent tricuspid valve involvement. Additional means to better assess the defect size and help optimize device selection could be explored in further trials. With increasing number of patients, an angiographic classification of the VSD morphology, similar to the one used for PDA closure, could also be helpful in this regard.

Due to the proximity of PM VSDs to the tricuspid valve, a device in this region may interfere with valve function, as seen in the catheterization laboratory in one of the authors' patients. Care must be taken to avoid excessive tension while advancing the sheath through the defect, which may result in tricuspid regurgitation. Entrainment with the tricuspid valve apparatus should be avoided by applying less tension to the delivery cable while retracting the sheath during right disc deployment. Apart from these technical considerations to minimize acute tricuspid valve dysfunction, tricuspid insufficiency caused by the presence of the device per se was not an issue in the midterm follow-up in the authors' and others experience [24-29]. However, the authors would agree that special attention should be paid to tricuspid valve function during follow-up, particularly due to the somewhat longer microscrew on the right ventricular disc, which may impinge on the septal leaflet.

The authors decided to close the PM VSDs in the patients with prolapse of the right aortic cusp was arbitrary. Although debatable, the authors believe that closing the shunt below the aortic valve will eliminate the Venturi effect that is likely to cause the prolapsing process. In addition, the device itself may theoretically offer some support for the prolapsing cusp. The authors would agree that long-term follow-up is mandatory to assess the adequacy of this strategy.

The authors believe that some of the technical difficulties and complications encountered in the series were due to a learning curve, also explaining the relatively high fluoroscopy times. Although the braided sheath was designed to avoid kinking, this happened in three patients. The authors anticipate that the same problem may also occur with smaller patients (less than 15 kg). Although permanent injury to the conduction system was not seen in the series, the occurrence of transient atrioventricular block and right and left bundle branch block observed in some patients should alert the physician for possible conduction abnormalities after device closure of PM VSDs.

The rate of complete closure after 6 months in the authors' and others series was over 95% [24-29]. This compares favorably with the rates achieved by surgical repair [3]. Ongoing endothelialization of the device should be responsible for the progressive decline in the rate of residual shunting with time.

In conclusion, it seems that the AMVO is suitable for closure of a wide range of PM VSDs of different sizes and morphologies with good short and mid-term outcomes [27].

**Current developments**

In order to improve precise placement of the device in the defect, some modifications on the device and delivery system have been made and tested in animals with encouraging preliminary results [30]. A screw with a female end was placed in the center of the left ventricular disc, opposite the female screw on the right ventricular disc. The rope wire was modified by placing a male screw at its tip. Before the device was advanced through the long sheath, the left ventricular disc was screwed on to the rope wire and the right disc to the delivery cable, as usual. Instead of removing the rope wire, it was used to create traction from the arterial side. In piglets, this enabled operators to place the device precisely in a much easier way, since it could be pulled back in the left ventricle with the rope wire when its position was suboptimal. Repositioning was also easier to perform because of the through-and-through cable-to-device-to-rope wire system, which could be manipulated by the arterial and venous ends. The device was deployed in the defect in the usual fashion and, after confirmation of its optimal position, the rope wire was unscrewed prior to unscrewing the delivery cable for device release.

These modifications may obviate some problems, such as kinking in the delivery sheath, accidental pull back to the right ventricle and inadvertent left ventricular injury, resulting in decreased fluoroscopy and procedural times. As such, this technique may be particularly useful in smaller children (< 15 kgs) and infants. The first successful human trials with this new system was presented as a live case at the *Seventh Pediatric Interventional Cardiac Symposium* in September 2003 in Orlando, FL, USA.

**Expert opinion**

From the evidence available, transcatheter closure of PM VSDs with the new AMVO is a feasible, safe and effective form of therapy with good short and midterm outcomes. Full echocardiographic skills and advanced interventional techniques are required for a successful and safe transcatheter closure. Longer follow-up and a larger number of patients are still needed to draw stronger conclusions. Special attention should be paid to
Five-year view

The next challenge for transcatheter closure of PM VSDs is to improve the device and delivery system in order to widen the scope of patient selection. Infants with large-sized defects will probably be managed safely and effectively with the evolving techniques [30]. In this regard, due to catheter and weight constraints, a transcatheter approach is unlikely to be performed in infants with excellent outcomes [11, 12]. A similar hybrid approach, employing an intraoperative transcatheter intervention in the bearing heart is likely to be undertaken for infants with large PM VSDs in the next few years.

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Key issues

- The isolated perimembranous (PM) ventricular septal defect (VSD) is one of the most common congenital heart malformations. Treatment has been classically indicated in the presence of significant left-to-right shunt, resulting in left ventricular overload.
- Surgery has been performed safely at very low rates of mortality, although it still involves morbidity, such as residual leaks, atrioventricular block, postcardiotomy syndrome and arrhythmias. In order to minimize these complications, transcatheter closure of PM VSDs has been attempted as an alternative approach to surgery.
- Recently, a device designed specifically for PMVSD closure has been developed: the Amplatzer Membranous VSD Occluder. Initial clinical experience has been very encouraging. The device is suitable to close a wide range of defect sizes and morphologies. The procedure is feasible with low risk, providing excellent occlusion rates (> 99%) for selected patients based on their weight.
- Further refinements in device design and delivery system are likely to widen the scope of patient selection and include smaller patients younger than 1–2 years of age. Although the procedure is associated with excellent short and midterm outcomes, longer follow-up and larger numbers of patients are needed to draw stronger conclusions. A randomized clinical trial is also required to compare the results of transcatheter closure with the standard surgical approach.

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Papers of special note have been highlighted as:

- of interest
- **of considerable interest


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- Animal model study forming the basis for perimembranous VSD closure in humans.